Trigger factors and mechanisms in migraine

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CHAPTER 4

EXPERIMENTAL HYPOXIA INDUCED ACUTE MOUNTAIN SICKNESS IS ASSOCIATED WITH INTRACELLULAR CEREBRAL OEDEMA. A 3 TESLA MAGNETIC RESONANCE IMAGING STUDY

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Abstract

Acute mountain sickness is common amongst not acclimatized persons ascending to high-altitude; the underlying mechanism is unknown, but may be related to cerebral edema. Nine healthy male students were studied before and after 6-hours exposure to isobaric hypoxia. Subjects inhaled room air enriched with N_2 to obtain SaO_2 values of 75-80%. Acute mountain sickness was assessed with the environmental symptom questionnaire, and cerebral edema with 3 Tesla magnetic resonance imaging in 18 regions of interest in the cerebral white matter. The main outcome measures were development of intra- and extracellular cerebral white matter edema assessed by visual inspection and quantitative analysis of apparent diffusion coefficients, derived from diffusion-weighted imaging, and B0 signal intensities, derived from T2-weighted imaging. Seven of nine subjects developed acute mountain sickness. Mean apparent diffusion coefficient increased 2.12% (baseline, 0.80 ± 0.09; 6-hours hypoxia, 0.81 ± 0.09; p=0.034), and mean B0 signal intensity increased 4.56% (baseline, 432.1 ± 98.2; 6-hours hypoxia, 450.7 ± 102.5; p<0.001). Visual inspection of magnetic resonance images failed to reveal cerebral edema. Cerebral acute mountain sickness scores showed a negative correlation with relative changes of apparent diffusion coefficients (r=-0.83, p=0.006); there was no correlation with relative changes of B0 signal intensities. In conclusion, isobaric hypoxia is associated with mild extracellular (vasogenic) cerebral edema irrespective of the presence of acute mountain sickness in most subjects, and severe acute mountain sickness with additional mild intracellular (cytotoxic) cerebral edema.

Introduction

Unacclimatized subjects, who rapidly ascent to high-altitude, may develop acute mountain sickness (AMS) that is characterized by headache, anorexia, nausea, vomiting, insomnia and dizziness[97,163-165]. The underlying mechanism for AMS is unclear. Intracellular (cytotoxic) cerebral edema, extracellular (vasogenic) cerebral edema, and increased cerebral blood volume have all been implicated, but without convincing scientific evidence [97,164,166]. Some magnetic resonance imaging (MRI) studies, using 1.5 Tesla machines, found that exposure to moderate hypo- or isobaric hypoxia, corresponding to altitudes of 4500 m, increased brain volume by 0.5-2.8% [167,168] and decreased cerebrospinal fluid volume in the lateral and third ventricles by 10.3% [169]. Results with respect to the presence and type of cerebral edema were, however, conflicting [167-170]. This could have been related to the relatively low resolution of 1.5 Tesla MRI and because the MR images were only visually evaluated and not analyzed with more sensitive quantitative methods.
In the present study, we used 3 Tesla MRI to investigate whether experimental hypoxia-induced AMS is associated with intra- and/or extracellular cerebral edema. We compared diffusion-weighted (DWI) and T2-weighted (T2WI) MR images obtained before and after 6-hours exposure to isobaric hypoxia by visual inspection and quantitative analysis of apparent diffusion coefficients (ADCs) derived from DWI, and B0 signal intensities derived from T2WI.

Materials and methods

Subjects

Nine healthy male volunteers (mean age 26.4 ± 3.5 years) were recruited from students of the University of Zurich, Switzerland. Exclusion criteria were: altitude exposure (>1500 m) in the previous 3 months, a history of smoking, substance and drug abuse, or of lung, cardiac, neurological or psychiatric disease, and contraindication to undergo MRI (e.g., pacemaker).
The local medical ethical committee approved the study protocol, and written informed consent was obtained from all subjects.

Study design

The study subjects were in supine position and were fitted a facial mask which was connected with a tube of 3 m length. The total flow of fresh gas varied between 9 to 12 liters per minute, because 6 liters of compressed air per minute were mixed with

3 to 6 liters of N_2 per minute. Thus, the stimulus was assumed to cause poikilocapnic hypoxia. Baseline examinations were done when the subjects were familiarized with the facial mask and the attached tube, and included assessment of the cerebral symptoms of AMS (AMS-C) by completion of the environmental symptom questionnaire (ESQ) [171], monitoring of arterial O_2 saturation (SaO_2), the measurement of the blood pressure, and baseline MRI. The supine subjects were then transported to a room adjacent to the MR suite, and the tube was connected with a gas container. Here, one investigator gradually increased the concentration of N_2 in the inspired air, over a period of 20 minutes, to obtain SaO_2 values of 75 to 80%. This corresponds to an altitude of about 4500 m. The SaO_2 values were measured using a fingertip pulse oximeter (Datex-Ohmeda, Helsinki, Finland). End-tidal pCO_2 was not determined for technical reasons. The SaO_2 was kept stable during the following 6 hours and the second MRI study by adjusting the mixture of inspired gas. After 6 hours of hypoxia, the subjects were transported in the supine position to the MR suite for the second MRI study. Symptoms of AMS and blood pressure were re-assessed every hour, and finally during the second MRI study.

MRI studies

MRI studies were performed using a 3 T Philips Intera whole body system (Philips Medical Systems, Best, The Netherlands). Identical protocols and volume positioning were used at baseline and during hypoxia. The DWI data were based on a spin-echo single excitation echo-planar imaging protocol. Whole brain scans with an in-plane resolution of 1.6 x 1.6 mm^2 (14 contiguous slices, slice thickness = 4 mm, matrix = 128^2, echo time = 79 ms, relaxation time = 3987 ms) were carried out along three orthogonal diffusion directions with a diffusion weighting of b = 1000 s/mm^2, of b=0 [172] and of B0 images (T2* weighted images from the same sequence, with no applied diffusion gradient). An isotropic diffusion-weighted image (Figure 3A) was calculated as the geometric mean of three orthogonal diffusion-weighted images. Additionally, for each slice a T2WI with minimal diffusion weighting (b < 20 s/mm^2) was acquired. The duration for the imaging procedure including the diffusion and the T2 protocol was 4 min and 6 s.

The MRI data were stored and independently analyzed after completion of the study by investigators who were not aware of the cerebral AMS (AMS-C) scores. Two physicists (TJ and UD) and neurologists (PSS and RWB), blinded to the AMS scores, looked for the presence of cerebral edema by comparing the second DWI and T2WI scans of each subject with the corresponding baseline scans (Figure 3). Another neurologist (ACN), also blinded to the AMS scores, measured the ADC values and B0 signal intensities in 22 regions of interest (ROI) as the average value of all pixels in the respective ROI.

The ROIs were circular and located on four consecutive slices (Figure 1). Slice A and B

were placed above, and the next two slices at the level of the cella media of the lateral ventricles. Eighteen of 22 ROIs were located in the cerebral white matter (nine in each hemisphere), and the other four in the cerebrospinal fluid (CSF) of both lateral ventricles. Cerebral white matter ROI were located in the anterior part in eight cases (beside the forceps minor; two measurements per slice), the middle part for two ROIs (beside the lateral ventricles; two measurements on the lowest slice), and the posterior part for eight ROIs (next to the forceps major, which corresponds to the lateral part of the corpus callosum fibers; two measurements per slice). Each white matter ROI consisted of 88 pixels, and each CSF ROI of 16 pixels. CSF ROIs contained fewer pixels than ROIs in the white matter, because not all ventricles were wide enough to accommodate larger circles. The use of smaller reference ROI in the CSF is appropriate, since the MRI signal is higher in the CSF than the white matter and thus provides a better signal-to-noise ratio. MRI signal intensities are arbitrary units with different absolute values at baseline and 6-hours sessions. Therefore, ROIs placed in the CSF were used to correct for intersession differences, because the CSF signal levels are assumed to remain unchanged during hypoxia. All ADC values and B0 signal intensities measured after 6-hours were thus corrected to achieve the same values in CSF as at baseline according to the proportion: $ROI_{6\text{-hours corrected}} = ROI_{6\text{-hours}} \times CSF_{baseline} / CSF_{6\text{-hours}}$, where CSF is the mean value of all CSF ROIs.

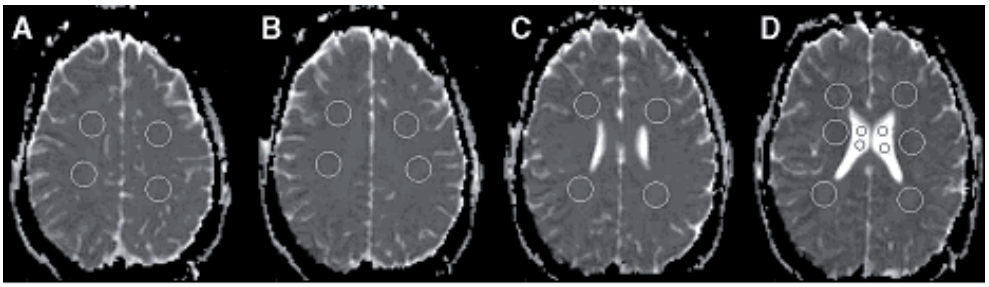

Figure 1 Axial T2-weighted MR images show the 22 regions of interest. Slice A placed above slice B, and slices C and D placed at the level of the cella media of the lateral ventricles.

Interpretation of ADC and B0 changes on MRI

Increase of both ADC and B0 values are indicative of extracellular (vasogenic) edema, whilst an increase of B0 values in combination with a decrease of ADC values is indicative for the development of intracellular (cytotoxic) edema [173-177].

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Assessment of AMS

The ESQ was translated to German and used as described previously [178]. Subjects were considered to suffer from AMS when the AMS-C score was ≥0.70[171] . The AMS-C score ranges from 0-5 and is based on eleven neurological symptoms.

Statistical analysis

Statistical analysis was performed using SPSS 12.0 (SPSS, Chicago, Illinois).

Mean ADC (primary outcome of the study) and B0 values obtained at baseline and after 6 hours were compared using a general linear model for repeated measurements including ROI location as covariate (total white matter ROI, n=162; anterior white matter ROI, n=72; middle white matter ROI, n=18; posterior white matter ROI, n=72). Associations between AMS-C scores and relative changes of ADCs and B0 signal intensities were assessed using the non-parametric Spearman correlation coefficients. P <0.05 was considered significant.

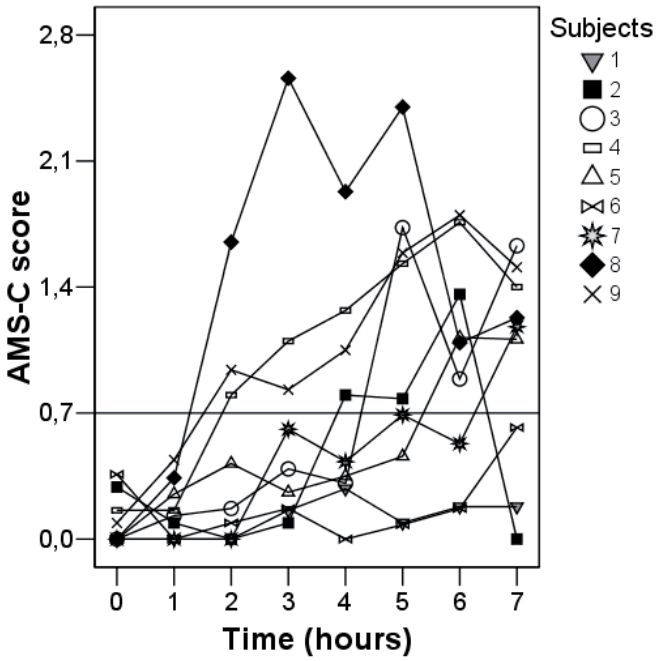

Figure 2 Cerebral acute mountain sickness (AMS-C) scores of all subjects at baseline and during hypoxia.

Results

All nine subjects completed the study. The data set was complete and was evaluated for all 9 subjects. Seven out of nine subjects (subjects 2-6, 8, 9) developed AMS during hypoxia. Six of the nine subjects had AMS during the second MRI scan (Figure 2). Baseline blood pressure did not differ between subjects with and without AMS. The mean AMS score of all subjects was higher at the time of MRI scanning than at baseline (Table 1). Systolic (baseline, 113 ± 9 mm Hg; during second MRI study, 115 ± 11 mm Hg; p=0.49) and diastolic (baseline, 72 ± 6 mm Hg; during second MRI study, 74 ± 4 mm Hg; p=0.71) blood pressure did not change during the study (values are means ± standard deviation).

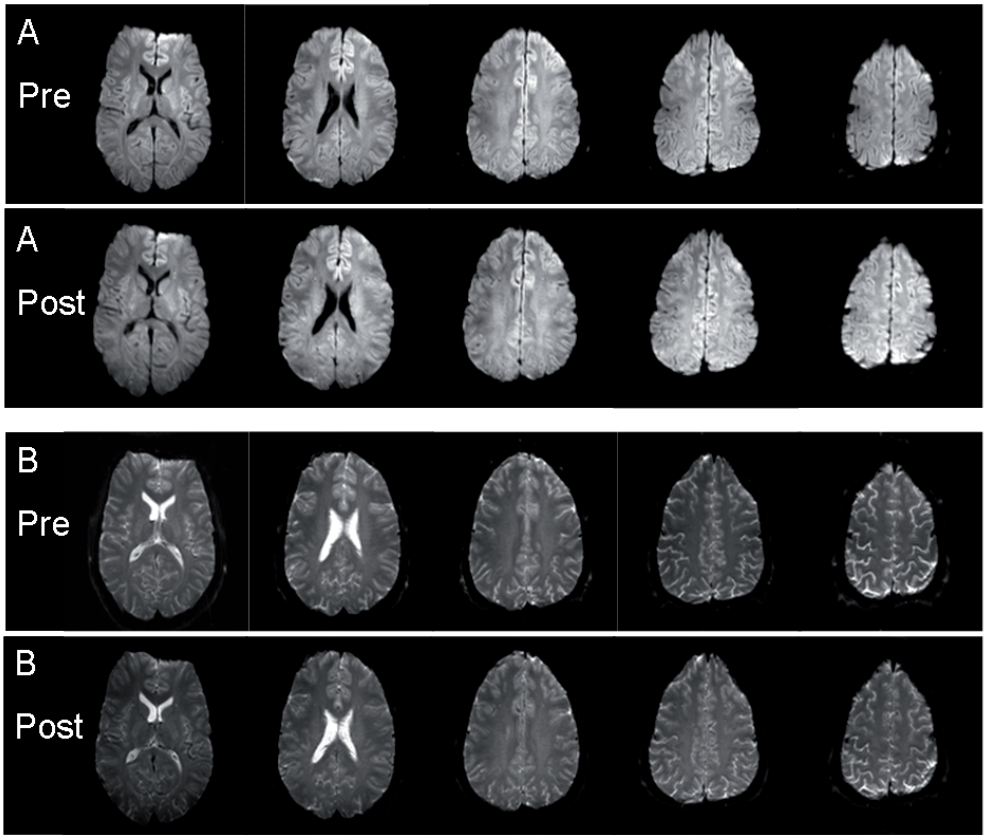

Figure 3 Axial diffusion-weighted (A) and T2-weighted (B) MR images obtained at baseline (upper rows) and after 6-hours exposure to hypoxia (lower rows) from subject 4 who suffered from severe acute mountain sickness. There is no evidence for the development of cerebral edema at visual inspection.

Table 1 Apparent Diffusion Coefficient Values at 3 Tesla MR Imaging in the Cerebral White Matter and Cerebrospinal Fluid, and Cerebral Acute Mountain Sickness Scores in Nine Healthy Subjects at Baseline and 6-Hours Exposure to Isobaric Hypoxia*

	ADC										
	Cerebral White Matter								CSF‡	AMS-C score	
	Anterior		Middle		Posterior		All			Score	
	Baseline	% Change at 6-h hypoxia†	Baseline	% Change at 6-h hypoxia†	Baseline	% Change at 6-h hypoxia†	Baseline	% Change at 6-h hypoxia†		Baseline	After 6-h hypoxia
Subject 1	0.70	7.72	0.66	-0.79	0.70	6.98	0.69	6.45	3.18	0.00	0.18
Subject 2	0.72	-5.11	0.71	-4.26	0.76	-3.40	0.74	-4.25	3.16	0.29	1.36
Subject 3	0.78	3.47	0.72	5.45	0.81	4.90	0.79	4.32	3.30	0.00	0.89
Subject 4	0.95	-7.27	0.92	-3.98	0.96	-6.53	0.95	-6.58	3.78	0.16	1.76
Subject 5	0.78	2.57	0.70	10.93	0.78	3.57	0.77	3.94	3.71	0.00	1.12
Subject 6	0.74	9.27	0.69	5.99	0.76	10.84	0.74	9.60	3.26	0.36	0.17
Subject 7	0.92	3.12	0.91	4.01	0.96	3.40	0.94	3.34	3.85	0.00	0.53
Subject 8	0.80	1.78	0.78	3.17	0.84	5.02	3.29	3.37	3.29	0.00	1.09
Subject 9	0.74	-0.20	0.70	0.06	0.75	-2.26	0.74	-1.09	2.78	0.09	1.80
Subjects 1-9 mean	0.79	1.71	0.75	2.29	0.81	2.50	0.80	2.12	3.37	0.10	0.99
SEM	0.03	0.90	0.03	1.20	0.03	0.88	0.09	0.57	0.35	0.05	0.20
Difference baseline vs 6 h at hypoxia							p=0.034			p=<0.01	

h denotes hours, and SEM standard error of the mean. * The concentration of N_2 in the inspired air was adjusted to obtain arterial SO_2 values of 75 to 80%. † The apparent diffusion coefficient values obtained before exposure to isobaric hypoxia were defined as 100% ‡ The values for the relative change of the apparent diffusion coefficient measured in the cerebrospinal fluid after 6-hours of isobaric hypoxia were zero, because they were corrected to achieve the same values as at baseline (for details see text).

MRI study

Visual inspection showed no evidence for cerebral edema (Figure 3).

Mean ADCs were increased by 2.12% (p=0.034, Table 1), and mean B0 values were increased by 4.56% (p<0.01, Table 2) after 6-hours exposure to hypoxia. The ADCs increased in 6 subjects (Figure 4), and B0 values in 8 subjects (Figure 5). ADCs (p=0.32) and B0 values (p=0.06) did not differ between the 3 white matter ROIs.

As shown in Figure 6, the AMS-C scores measured after 6-hours exposure to hypoxia showed a negative correlation with the relative change of ADC values (Spearman correlation coefficient -0.83, p = 0.006). There was no association between the AMS-C scores measured after 6-hours exposure to hypoxia and the relative change of B0 values (Spearman correlation coefficient -0.22, p = 0.576; Figure 7).

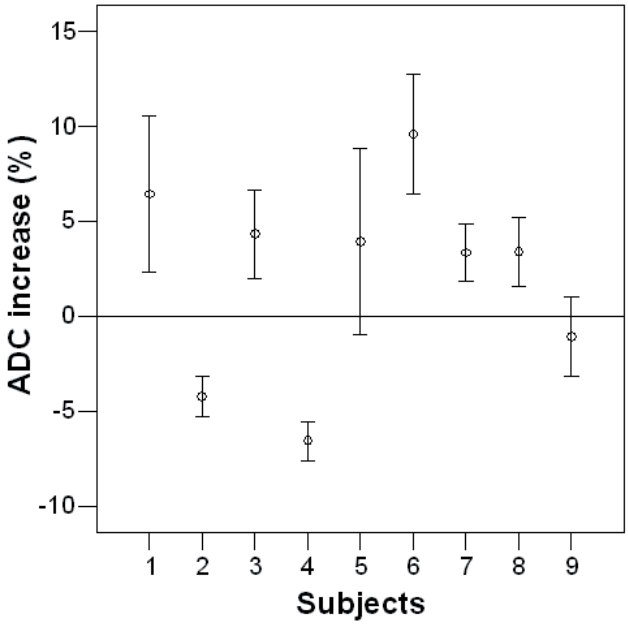

Figure 4 Relative changes of the apparent diffusion coefficient (ADC) after 6 hours of hypoxia compared to baseline in all nine subjects.

Table 2 B0 Values at 3 Tesla MR Imaging in the Cerebral White Matter and Cerebrospinal Fluid, and Cerebral Acute Mountain Sickness Scores in Nine Healthy Subjects at Baseline and 6-Hours Exposure to Isobaric Hypoxia*

	B0 value									AMS-C score	
	Cerebral White Matter								CSF‡		
	Anterior		Middle		Posterior		All			Score	
	Baseline	% Change at 6-h hypoxia†	Baseline	% Change at 6-h hypoxia†	Baseline	% Change at 6-h hypoxia†	Baseline	% Change at 6-h hypoxia†		Baseline	After 6-h hypoxia
Subject 1	186.13	8.27	224.00	8.11	216.38	2.13	203.78	5.52	879.00	0.00	0.18
Subject 2	354.25	0.42	389.00	6.74	370.75	11.36	365.44	5.98	1353.75	0.29	1.36
Subject 3	452.38	10.86	489.50	12.37	441.75	11.10	451.78	11.13	1630.75	0.00	0.89
Subject 4	475.75	-4.97	488.00	1.16	490.50	0.93	483.67	-1.67	1544.00	0.16	1.76
Subject 5	489.63	5.23	569.00	6.54	563.88	4.08	531.44	4.87	2019.50	0.00	1.12
Subject 6	411.13	1.61	445.00	3.89	430.13	7.77	423.33	4.60	1477.75	0.36	0.17
Subject 7	469.25	1.92	502.50	3.50	508.63	0.80	490.44	1.60	1580.75	0.00	0.53
Subject 8	478.38	4.37	498.50	1.60	464.50	11.07	474.44	7.04	1724.00	0.00	1.09
Subject 9	439.50	6.03	504.00	7.09	479.13	-3.46	464.28	1.93	1373.75	0.09	1.80
Subjects 1-9 mean	417.38	3.75	456.61	5.67	440.63	5.09	432.07	4.56	1509.25	0.10	0.99
SEM	32.11	1.55	33.25	1.18	33.26	1.81	32.45	1.22	103.30	0.05	0.20
Difference baseline vs 6 h at hypoxia							p=<0.01			p=<0.01	

h denotes hours, and SEM standard error of the mean. * The concentration of N_2 in the inspired air was adjusted to obtain arterial SO_2 values of 75 to 80%. † The apparent diffusion coefficient values obtained before exposure to isobaric hypoxia were defined as 100% ‡ The values for the relative change of the apparent diffusion coefficient measured in the cerebrospinal fluid after 6-hours of isobaric hypoxia were zero, because they were corrected to achieve the same values as at baseline (for details see text).

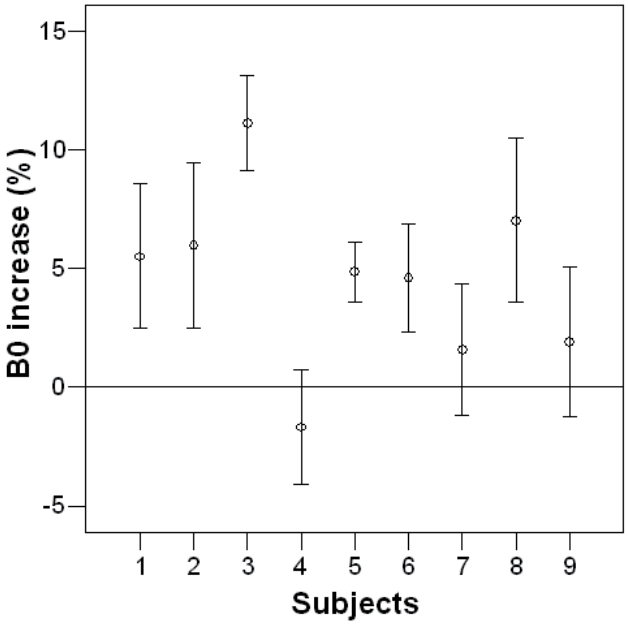

Figure 5 Relative changes of the B0 values after 6 hours of hypoxia compared to baseline in all nine subjects.

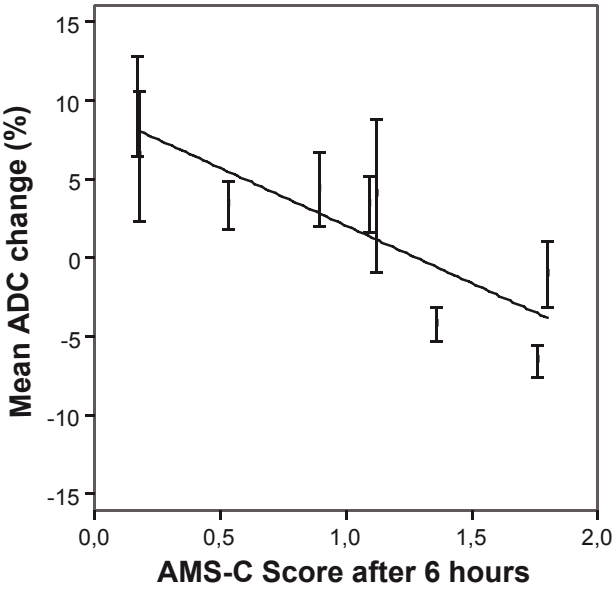

Figure 6 The mean value of two cerebral acute mountain sickness (AMS-C) scores measured immediately before and after MR imaging performed at hypoxia showed a weak but significant negative correlation with the relative change of the apparent diffusion coefficient (ADC).

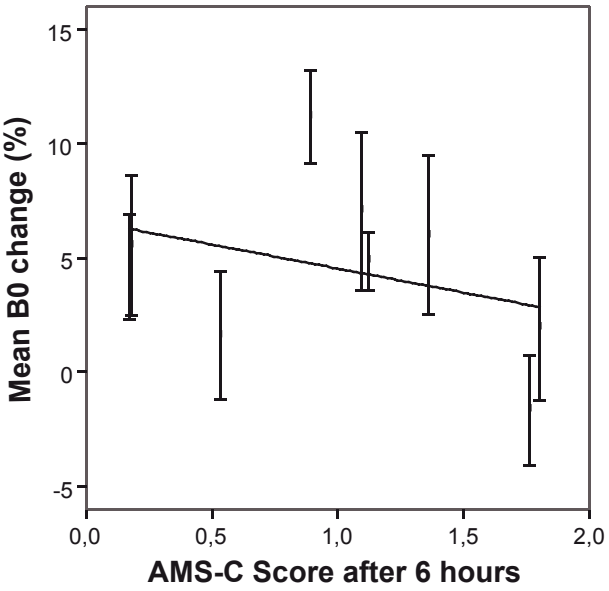

Figure 7 The mean value of two cerebral acute mountain sickness (AMS-C) scores measured immediately before and after MR imaging performed at hypoxia showed no correlation with the relative change of the B0 signal intensity values.

Discussion

In the present 3 Tesla MRI study, we found that experimental isobaric hypoxia for six hours: 1) caused AMS in seven (77%) of nine healthy volunteers; 2) produced a mild extracellular (vasogenic) cerebral edema, irrespective of the presence of AMS, which was identified by a small increase of both ADCs and B0 values, whereas visual inspection of the MRI data failed to detect any differences; and 3) that the AMS-C scores were negatively correlated with the ADC values. The prevalence of AMS in this series is in accordance with the results of two previous studies exposing 31 subjects to isobaric hypoxia corresponding to altitudes of 4500-4564 m during 9-16 hours [167,179]. In the study of [179], 6 (67%) of 9 subjects developed AMS, and in the study of [167] 11 (50%) of 22 subjects were affected by this altitude illness.

The fact that the mild extracellular (vasogenic) cerebral edema was just detected by quantitative but not visual analysis of the MRI data is in accordance with the results obtained in three 1.5 T MRI investigations [167-169]. These studies found no cerebral edema at visual inspection of T2WI and DWI in 41 subjects with mild to moderate AMS who were exposed to hypobaric or isobaric hypoxia corresponding to altitudes of 4500-

4572 m for 10 to 32 hours[167-169]. Furthermore, one of these 3 studies found a mild extracellular cerebral edema with increased B0 values and a trend for decreased ADCs [167] . The higher resolution and signal-to-noise ratio of 3 Tesla MRI used in the present study makes it more sensitive for detecting cerebral abnormalities[180] than 1.5 Tesla MRI employed in previous AMS investigations [167-169]. Despite this, visual inspection even of 3 Tesla MRI brain images was still not sensitive enough to detect the cerebral edema associated with AMS. This is in sharp contrast to high altitude cerebral edema (HACE). Here visual inspection of proton density- and T2-weighted MRI brain images revealed extracellular edema of the white cerebral matter at a mean of 58 hours (range, 16 to 132 hours) after the onset of HACE symptoms [104].

There was no association between AMS-C scores and BO signal intensities in this series, which confirms the results of a previous study [167]. In this respect it is important to note that, in reality, the degree of extracellular brain edema might have been higher. The B0 signal intensity increase due to cerebral edema may have been neutralized by the blood-oxygenation-level-dependent (BOLD) effect of hypoxia [181,182]. This effect is related to the intravascular concentration of deoxyhemoglobin, which lowers signal intensity of B0 images by increasing magnetic susceptibility [183-186]. As hypoxia will increase the intravascular concentration of deoxyhemoglobin, it will also lower the intensity of the B0 signal and thus the level of perceived cerebral edema. Therefore, the BOLD effect might have prevented the detection of an association between the B0 values and the AMS-C scores. Consequently, it cannot be completely excluded that the mild extracellular cerebral edema is in part responsible for AMS, e.g. by stimulating pain sensitive fibers in the meninges, the meningeal and pial vessels [187]. A potential role of vasogenic cerebral edema is underscored by two observations: Symptoms and signs of AMS as well as abnormal B0 values and ADCs occurring during exposure to isobaric hypoxia disappeared after the subjects were re-exposed to normoxia [167], and corticosteroids, which reduce extracellular cerebral edema, are an established therapy of AMS [188].

The third and most important result of the present study is based on the observation that subjects with the most severe AMS symptoms showed the lowest ADC values. Being in accordance with findings reported by [167], this would suggest that severe AMS is associated with intracellular (cytotoxic) edema of the cerebral white matter, on top of hypoxia-driven extracellular (vasogenic) edema. The cytotoxic edema may have been caused by a decreased activity and/or expression of the Na+, K+-ATPase in the cerebral white matter [189-191]. A reduction of ATPase activity is associated with reduced levels of tissue ATP and a shift from aerobic to anaerobic glycolysis, and lactate is built up causing acidosis[189,191,192]. Using declining intracellular pH (pHi) as an indicator of increased intracellular lactate production, ^{31}P MR spectroscopy (MRS) studies observed a pHi

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decline at arterial PO_2 (PaO_2) values of 30-45 mm Hg [189,191,193]. We observed PaO_2 values of 40-45 mm Hg in subjects exposed to an altitude of 4559 m [178,194] . Consequently, the subjects investigated in this series were exposed to levels of hypoxia, which might lead to PaO_2 values causing anaerobic glycolysis and reducing the cerebral metabolic rate of oxygen ($CMRO_2$), although no study has shown a decrease of $CMRO_2$ in humans exposed to high altitude [195,196] . However, the study of [196] was performed at a lower altitude of 3800 m, and the investigation of [195] in subjects who were chronically exposed to high altitude. More important is that a recent study comparing MRI with positron emission tomography (PET) findings in patients with acute ischemic stroke has shown that ADCs are not reliable predictors of reduced $CMRO_2$ at the levels of hypoxia applied in our subjects [197]. These PET findings question the assumption that more severe forms of AMS are associated with intracellular (cytotoxic) edema. Further studies assessing also the $CMRO_2$ in the cerebral white matter are needed to answer this question.

The study is limited by the low number of included subjects. Furthermore, the present findings may not be applicable to hypobaric hypoxia, because the severity of AMS has been shown to be increased during simulated altitude compared with isobaric hypoxia[179].

We conclude that experimental isobaric hypoxia is associated with mild extracellular (vasogenic) cerebral edema irrespective of the presence of AMS in the majority of subjects, and severe AMS with additional mild intracellular (cytotoxic) cerebral edema.