Cerebral hemodynamics and fluid shifts during normobaric hypoxia

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Introduction:

Acute exposure to hypoxia at high-altitude can result in symptoms of high-altitude illness. Acute mountain sickness (AMS) is the most common clinical form and manifests with symptoms of headache, nausea, vomiting, anorexia, dizziness, lethargy, fatigue, and sleep disturbances 6-12 hrs after exposure. Although more common at higher elevations (>2500m), symptoms may appear much lower and individual susceptibility appears to play a significant role. Cerebral edema as a cause of AMS symptoms has been hypothesized since 1969. However, the complete pathophysiology remains unclear. Vasogenic edema in the splenium of the corpus callosum has been reported in severe AMS [1], however the clinical (and radiological) picture is mixed. We hypothesize that changes in cerebral physiology should be detectable - particularly in subjects in the AMS-susceptible population before clinical symptoms manifest. We looked specifically for changes in CBF, tissue water content or changes in the intracerebral CSF volume fraction. To address this prospectively we designed a study to measure BOLD, CBF, T_2 and CSF volume before and following hypoxic exposure (12.75% O_2).

Methods:

Data were collected on a GE Signa 3T system. Perfusion/BOLD measurements were made in two healthy subjects. We used 4 cycles of 16 min periods: 8 min breathing normal air and 8 min breathing 12.75% oxygen. A dual echo, gradient echo PICORE QUIPSS II [2] spiral EPI sequence was used to measure both the BOLD and perfusion responses continuously during the 64 min experiment. Sequence parameters were: T_R =5s, TI1=700ms, TI2=1400ms, TE=9.2ms and 30ms, FOV=24cm, matrix size=64x64, 5 contiguous 6mm slices. Slices were positioned axially, parallel to the genu/splenium of the corpus callosum. A perfusion-weighted time series was created using the first echo data. The BOLD time series was created using the second echo. Each BOLD/perfusion-weighted time series (768 images, 5s resolution) was correlated to the stimulus paradigm on a pixel-by-pixel basis. To address T_2 and CSF volume changes, one individual was exposed to 3 hours of hypoxia. T_2 of cerebral tissues was calculated from 7 echos of a FSE sequence acquired axially at the same level through the corpus callosum. Four slices of 5mm, FOV =24cm, matrix 256x256, T_R= 10s, T_E = 8, 17, 35, 149, 297, 594, 1188ms. A double exponential function was fitted to the data, and the M0 components used to calculate the CSF and brain water content changes for gray and white matter. For CSF volume measurement, we acquired a 3D T_1 image used to segment intracranial CSF+ Brain. This mask was then applied to a heavily T_2-weighted 3D FSE dataset T_E 400 T_R 3000 256x256x124 (1mmx1mmx1.2mm) to measure volume of CSF directly. Continuous physiological monitoring of the end-tidal CO_2, heart rate and peripheral oxygen saturation was also carried out.

Results.

In both subjects, there was a strong, global BOLD response; image signal intensity decreased during hypoxia and returned to resting state during the periods of normoxia. However, we were not able to detect a significant change in parenchymal perfusion. One subject did show increased perfusion in choroid plexus. Following 3 hours of hypoxia exposure, there was a 5% decrease in intracranial CSF volume from 332.7mm^3 to 316.5 mm^3. This was accompanied by a shift in the tissue water and CSF components in the white matter. Brain water in white matter increased 1.5%, and CSF content increased 6.5% following hypoxia exposure. In gray matter, CSF and tissue water increased 1.89% and 3.2% respectively. Of note, CSF fraction increased 11% in the splenium of the corpus callosum.

	M0 (short T_2)	%Tissue water change	M0 (long T_2)	% CSF change
GM (21% O_2)	992	3.21	1218	1.86
GM (12.75% O_2)	1056		1280	
WM (21%)	829	1.52	1004	6.55
WM (12.75%)	868		1104	
Splenium (21%)	981	-6.12	1073	11.39
Splenium (12.75%)	951		1234	

Discussion.

These preliminary results fit with our hypothesis of subclinical alterations in cerebral physiology during hypoxic exposure. Although a perfusion change was not directly detectable in cerebral parenchyma, there was a more global increase in perfusion in the choroid. Following prolonged hypoxia, there is evidence of fluid shifts, in the cerebral parenchyma. This is observed in the splenium of the corpus callosum in keeping with earlier reports of a predilection for fluid shifts in this area during severe altitude sickness. There was also subclinical increase in brain volume, as evidenced by a decrease in the intracranial CSF volume fraction. It is hypothesized that this change will remain subclinical until the shift in CSF can no longer compensate for the change in cerebral volume [3]. These results underscore the utility of MRI in evaluating the normal physiological response to hypoxia. High altitude illness also provides a versatile model for studying any etiology of cerebral hypoxia.

References. [1] Hackett, PH JAMA 1998;280:1920. [2] Wong et al., Magn Reson Med 1998:39:702. [3]Roach, RC. J Exp Bio 2001;204:3161.