

## Combined diffusion and T<sub>2</sub> parameter measures identify early onset cytosolic oedema in simulated altitude induced hypoxia

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### Introduction

Exposure to the hypoxic environment at moderate altitude (2500 – 4500 m) is often followed by the development of Acute Mountain Sickness (AMS), which presents as a number of symptoms including headache, gastrointestinal upset, and fatigue. Understanding the pathophysiology of AMS will be beneficial to clinicians involved in high altitude medicine. The purpose of this study was to use MRI to study possible cerebral water compartment changes during prolonged hypoxia as experienced during a stay at altitude. Utilising a multi-direction diffusion weighted imaging sequence and a multi-echo T<sub>2</sub>W magnetic resonance imaging sequence we evaluated changes in fractional anisotropy (FA), mean diffusivity (MD) and T<sub>2</sub> relaxation resulting from a hypoxic environment similar to that found at 4500 m after 2 and 10 hrs of exposure.

### Methods

A total of 13 male (age = 26 (SD 6) yrs; body mass = 77 (SD 12) kg; height = 182 (SD 9) cm) volunteers took part after informed consent was attained. Exclusion criteria were any clinically diagnosed primary headache disorder and ascent to altitude above 1500 m in the previous 6 months. This study was approved by the Bangor University Ethics Committee and conformed to the Declaration of Helsinki (2008). Participants were scanned during exposure to either normoxic or hypoxic atmosphere (2 and 10 hrs after onset in each case) on two separate days (at least 5 days between each condition)

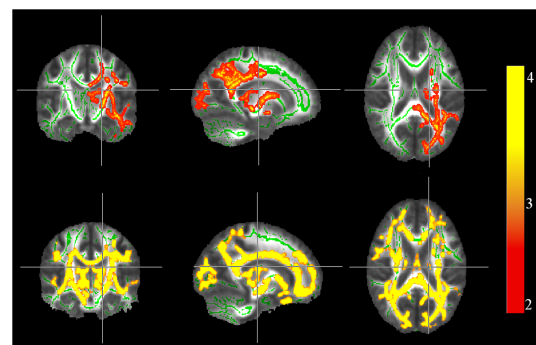
T<sub>2</sub> relaxation time was calculated for the whole brain as a mono-exponential function using a multiecho sequence (TE, 20ms, 40ms, 60ms, 80ms and 100ms, field of view 200; slice thickness 2.00 mm; acquisition matrix 240 x 234; voxel dimension 1.0 x 1.0 x 2.0 mm; TR 7,297, flip angle 90°). A diffusion-weighted, spin-echo, single-shot, echo-planar imaging sequence (34 gradient directions with b values set at 0 and 800s.mm<sup>2</sup>, field of view 220 x 220; slice thickness 2.00 mm; number of slices 64; acquisition matrix 112 x 110; voxel dimension 1.5 x 1.5 x 1.5 mm; TE 70; TR 8,552, flip angle 90°) was then collected for measurement of the FA and MD Using the FMRIB's Diffusion Toolbox (FDT v2.0) part of FSL 4.1.9<sup>1</sup>. TBSS was then used to allow whole brain comparisons between normoxia and each hypoxic time point. Exploratory regional analyses were also carried out.

### Results

Voxel-wise analysis using TBSS revealed a significant reduction in MD throughout the left posterior hemisphere after 2 h in hypoxia (see figure 1, top panel). Furthermore, after 10 h in hypoxia, TBSS identified extensive reductions in MD supratentorially throughout the cerebral white matter (see figure 1, bottom panel). In contrast, no significant differences in T<sub>2</sub> relaxation or FA were observed at either time point. Exploratory t-tests of a ROI based analysis revealed that FA was significantly elevated in the centrum semiovale ( $\Delta 0.02$ ,  $t = 2.25$ ,  $P = 0.05$ ), and posterior white matter ( $\Delta 0.02$ ,  $t = 3.04$ ,  $P = 0.01$ ) and a focal reduction in T<sub>2</sub> relaxation within the frontal lobe ( $\Delta -2.68$  ms,  $t = 2.84$ ,  $P = 0.01$ ) and posterior white matter ( $\Delta -3.30$  ms,  $t = 2.25$ ,  $P = 0.05$ ) after 2 and 10 h respectively.

### Conclusions

The decrease in MD with associated focal changes in FA and T<sub>2</sub> relaxation indicate that acute moderate hypoxia results in the movement of water from the freely diffusing extra-cellular space to the more restricted intracellular space, and does not involve substantial increases in interstitial water content from vasogenic oedema. These results add to our understanding of potential pathophysiology of illness at altitude, and the sequelae of oedematous events in hypoxia.



**Figure 1** - TBSS analysis of DTI data showing MD reductions at 2 hrs (top) and 10 Hrs (bottom) after introduction to a simulated high altitude environment (Hypoxia).

1. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM & Behrens TEJ (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *NeuroImage* **31**, 1487–1505.