Changes in cerebral blood flow and vasoreactivity to CO2 after 7 days at 4400 m

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Introduction

Over the first hours of hypoxic exposure, minor changes in cerebral blood flow (CBF) are observed, depending on the net effect of hyperventilation-induced hypocapnia (*i.e.* a vasoconstrictor stimulus) and the level of hypoxia (*i.e.* a vasodilator stimulus)[(1)]. With more prolonged hypoxia (several days), CBF at rest may return to values observed in normoxic conditions, depending on changes in blood gases and cerebrovascular reactivity with acclimatization. Changes in cerebral perfusion and CO_2 cerebrovascular reactivity at sea level in the hours following a prolonged stay at high altitude remain however unclear. The aim of the present study was to assess the effects of 7 days at 4400 m on cerebral perfusion and cerebro-vascular reactivity (CVR) to CO_2 by arterial spin labelling magnetic resonance imaging at sea level.

Methods

Eleven healthy male subjects, non-acclimatized to altitude, stayed for 7 days at 4400 m (Observatoire Vallot, massif du Mont-Blanc). Before and within 6 h after returning to sea level, subjects were investigated using Pseudo-Continuous ASL at 3 T (Philips Achieva TX scanner) during a block-design inhalation paradigm to extract CO_2 vasoreactivity and basal cerebral perfusion images.

Acquisitions, performed with a 32-channel head-only receive array, included a T_1-weighted structural image, an ASL reference scan and one series of pseudo-continuous ASL data (2) (WET pre-saturation, 1650 ms label, 1525 ms post-label delay) using a multi-slice single-shot EPI readout (3x3x6 mm^3, 20 slices, TE 12 ms, sense-factor 2.5) with a TR of 4 s for a duration of 12 min. Capnia was modulated in a 1/2/1-min paradigm (3 cycles) by alternating air and an air/CO_2 mixture (7% CO_2, 21% O_2, balance N_2) administered at 12 l/min via a high-concentration face mask. End-tidal CO_2 was measured via nasal cannula using an MR-compatible capnometer, and recorded together with scanner triggers for synchronization in order to build a regressor representing the physiological response to hypercapnia for use in the data analysis[(3)]. Respiratory rate, heart rate and oxygen saturation were also recorded during the exam. Physiologic data acquired during periods of air and air/CO_2 were averaged separately in the analysis ($\Delta EtCO_2 = EtCO_{2,Hypercapnia} - EtCO_{2,Baseline}$).

Data were analysed using Matlab, the SPM software and custom routines. Images were realigned after removing any systematic bias in realignment parameters between tag and control images. Frames exhibiting strong motion were marked for exclusion from the subsequent analysis. Structural images were segmented and all images were normalised to the MNI template. Functional data were smoothed in 3D using a 6-mm Gaussian kernel. ASL signal amplitude was scaled to express the difference between control and tag images in units of ml/100g/min.

Outliers in hypercapnia data were discarded and data were interpolated to the pCASL volume acquisition times, taking lag due to dead space in the sample line into account. Baseline perfusion was modelled with a regressor alternating between 0.5 and -0.5 for control and tag images respectively throughout the scan. Hypercapnia-related perfusion increase (vasoreactivity) was modelled with a baseline-corrected capnia regressor (ctl/tag modulated for perfusion, unmodulated for BOLD). CVR was expressed as percent change in perfusion per mmHg change in $EtCO_2$. In order to compare perfusion values between pre- and post-acclimatization sessions at identical capnia states, isocapnic perfusion maps were calculated on a voxel-by-voxel basis for the post-acclimatization session for each subject as follows: $Perf_{Post\text{-}isocapnic} = Perf_{Post,Baseline} \cdot (1+CVR_{Post} \cdot \Delta EtCO_2)$.

For each scan, a ROI was defined including all voxels with a grey-matter (GM) fraction of at least 70% for the perfusion analyses in the vascular territories of the left and right middle cerebral arteries (MCA) and in the anterior and posterior territories. The vasoreactivity analysis was based on the same ROIs, further constrained to voxels in which significant baseline perfusion was detected ($p<0.05$ FWE). ROI-average response amplitudes were computed for the two sessions before and after one week at 4400 m (pre/post altitude acclimatization).

Tab 1	$EtCO_2$ baseline	$EtCO_2$ hypercapnia	$\Delta EtCO_2$
Pre	**40.9 ± 4.9**	**51.1 ± 3.3**	**10.2 ± 3.6**
Post	**33.2 ± 4.0**	**44.2 ± 3.4**	**11.0 ± 3.6**

Results

Data from one subject were excluded from the analysis for excessive motion in the MRI.

The difference between pre- and post-altitude sessions in respiratory rate, heart rate and oxygen saturation was not significant, for both air and air/CO_2 conditions. However, we saw a significant decrease post-altitude in $EtCO_2$ under air ($p<0.001$) and under hypercapnia ($p<0.001$), with a constant $\Delta EtCO_2$ response to the capnic challenge (Tab 1).

For 8 out of 10 subjects perfusion in the MCA territory was significantly higher in the post-altitude condition (Fig 1). This perfusion increase was however not significant at the group level, with a p-value of 0.07 (paired t-test). The increase in perfusion was less pronounced in the other territories (Fig 2). Correction of the CBF maps for capnic differences based on measured CVR considerably increased the difference between pre- and post-altitude perfusion. The isocapnic perfusion change was highly significant at the group level in the MCA and anterior territories ($p<0.001$) (Fig 2,4). Cerebral vasoreactivity, expressed in percent perfusion change per mmHg change in capnia, seems to decrease after 7 days at 4400 m, but the difference does not reach significance at the group level (Fig 3).

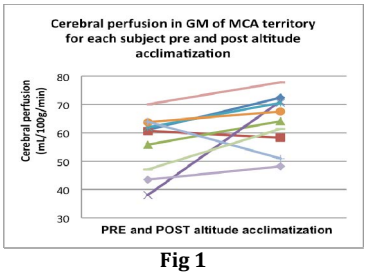

Fig 1

Conclusion

We hypothesized that following altitude exposure, cerebral perfusion would be increased while CO_2 cerebrovascular reactivity would be enhanced as a consequence of high altitude acclimatization. Cerebral blood flow did increase in most subjects, but CVR remained constant or decreased slightly. Meanwhile, end-tidal CO_2 significantly decreased after acclimatization to high altitude probably due to persistent hyperventilation [(4)]. By correcting for these capnia changes, we showed that isocapnic perfusion is increased by up to 40% after 7 days at 4400 m, without affecting vasoreactivity to CO_2. A potential mechanism for the long-term effect of exposure to altitude on CBF is a change in blood electrolyte concentrations affecting blood pH [(5)].

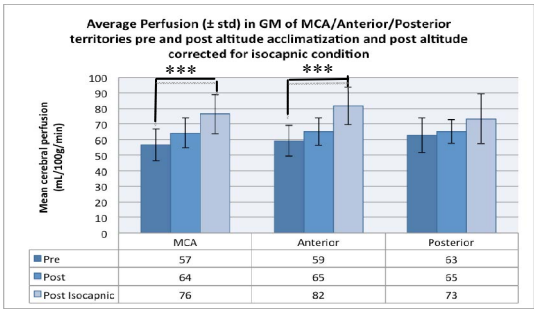

Fig 2

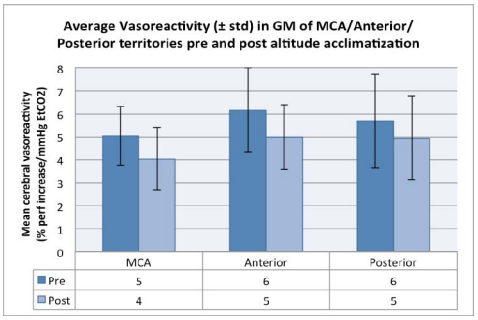

Fig 3

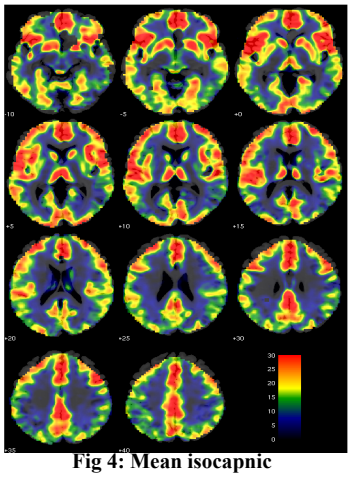

Fig 4: Mean isocapnic perfusion difference between pre- and post-altitude acclimatization

References [(1)]Brugniaux et al., *Resp Physiol Neurobiol 158:212*, 2007 [(2)]Dai et al., *Magn Res Med 60:1488, 2008* [(3)]Villien et al., ISMRM2011, poster 2103 [(4)] Masuyama et al., *J Appl Physiol* 61(2) : 500-506, 1986 [(5)] Powell et al., *Resp Physiol 112:123*, 1998