Sustained hypoxia attenuates CBF and BOLD activation in visual cortex

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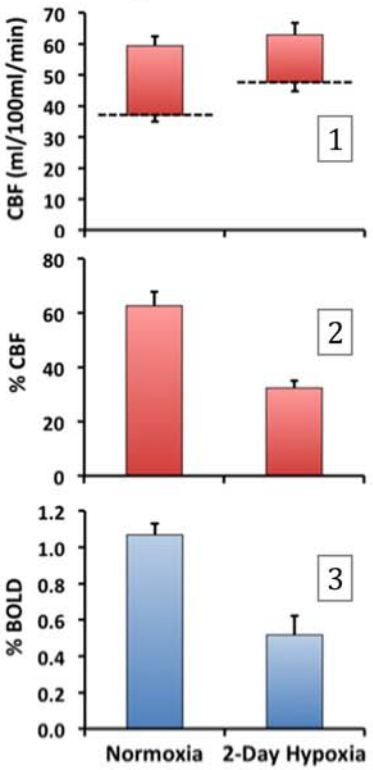
Target Audience: Researchers and physicians interested in the physiology of cerebral hypoxia

Purpose: Currently we have only a limited understanding of the effects of acclimatization to sustained hypoxia on cerebral blood flow (CBF) and cerebral O_2 metabolism ($CMRO_2$), including both baseline effects and the impact on dynamic responses to neural stimuli. In previous studies we found an increase in resting CBF [1] and an increase in resting cerebral O_2 metabolism ($CMRO_2$) [2]. To assess how neurovascular coupling is impacted by sustained hypoxia, we examined the CBF and BOLD responses to a stereotypical flickering checkerboard during normoxic baseline conditions, and following 48 hrs acclimatization to high altitude hypoxia.

Methods. CBF / BOLD visual activation was measured in 27 healthy volunteers (16 M, 11 F, mean age 27±7.5). Measurements were made on a GE 3T scanner. CBF/BOLD used a dual echo PICORE QUIPSS II ASL technique (TE1 9ms, TE2 30ms, TI 700ms, TI2 1500ms, TR 2.5s, FOV 240, 64 x 64 matrix, six 7 mm axial slices centered on calcarine fissure). Stimulus was 4 cycles of 20 seconds 8Hz flickering checkerboard interspersed with 60 seconds neutral gray screen. 2 acquisitions – the first used as a functional localizer to define visual cortex, the second used for data analysis. High resolution 3D-T1w axial FSPGR MRI was used to define ROI and rotate individual scans into standard space (ICBM) (TE=4.2ms, TR=10.1ms, TI=450ms, bandwidth 20.83kHz, FOV 25 x 25 x 16 cm, matrix 256 x 256 x 128, ~1mm x 1mm x 1.3mm resolution). Time series were corrected for motion and physiological noise. Additional measures of CSF relaxation and coil homogeneity were acquired to quantify absolute CBF from the ASL signal. After an initial MRI in normoxia, subjects travelled to 3800m altitude, and remained hypoxic (FiO2 = 90 Torr) for 48 hrs until the second MRI was completed. Significant changes from normoxia assessed with t-test (2-tailed, alpha = 0.05).



Results: After 2 days of hypoxia, baseline CBF was increased by 30% (figure 1, dashed line) and the fractional change in CBF in response to the stimulus decreased by 50% (figure 2). Interestingly, this led to the absolute CBF during the stimulus to be similar in both normoxic and hypoxic conditions (figure 1). The BOLD response to the stimulus was also reduced by 50% (figure 3). Results are summarized in the table (mean ±SEM).

Discussion: Although there have been several studies of how the BOLD response is altered by acute hypoxia, there have been few looking at acclimatization and combining measurements of BOLD with CBF. Several hemodynamic changes that accompany hypoxia would be expected to impact the magnitude of the BOLD activation. The BOLD response is primarily driven by the CBF change, but is modulated by three additional factors: 1) the amount of deoxyhemoglobin present in the baseline state; 2) the coupling ratio of the CBF and $CMRO_2$ responses to the stimulus; and 3) the degree of blood volume increase that serves to alter total deoxyhemoglobin. Hypoxia is expected to affect #1 (with the increased amount of baseline deoxyhemoglobin tending to increase the BOLD response for the same CBF change), and #3 (with SaO_2 of 83%, the arterial blood is partially deoxygenated, and arterial volume changes with activation would be expected to have a negative effect on the BOLD signal). In these data, though, the reduction of the BOLD response can be explained just by the reduction of the fractional CBF response alone, suggesting that the other effects are essentially self-canceling. Interestingly, this reduction of the fractional CBF change is not because the absolute CBF during the stimulus was decreased (the values in normoxia and hypoxia were similar) but rather because of the rise of CBF in the baseline state prior to the stimulus. These results demonstrate the complexity of understanding BOLD responses after acclimatization to hypoxia, and illustrate the richer context provided by simultaneous measurements of CBF.

	SaO2 (%)	*CBF (Baseline) (ml/100ml/min)*	*CBF (Activation) (ml/100ml/min)*	*% CBF (%)*	*% BOLD (%)*
Normoxia:	*98±0.2*	*37±2*	*59±3*	*63±5*	*1.1±0.06*
2-Days Hypoxia:	*83±1.2*	*48±3*	*63±4*	*32±3*	*0.5±0.1*
*(** P ≤0.01)*	**	**		**	**

References: [1] Dyer et al. 2008 Resp Physiol Neurobiol: 160:267-276 [2] Smith et al. J Appl Physiol 2013. Supported by: NIH NS053934 (DJD) NIH NS075812 (DJD)