Validating the Physiological Assumptions Made in Hyperoxia Calibrated BOLD

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Introduction: Recently, the use of hypercapnia to calibrate BOLD fMRI signals for the estimation of $CMRO_2$ has been questioned, as this may be confounded by an associated reduction in neuronal activity [1, 2] and $CMRO_2$ [3]. As hyperoxia for BOLD calibration becomes more widely used due to the increased precision and tolerability by subjects [4], it is important to assess whether similar confounds exist. It is often assumed that hyperoxia leads to vasoconstriction causing a global decrease in cerebral blood flow (CBF) [5,6,7], and potential affecting cerebral blood volume (CBV) [6]. However, in prior studies it is not clear whether hyperoxia is the single contributory factor, since may have been accompanying mild hypocapnia [8]. Here, by independently controlling end-tidal concentrations of CO_2 and O_2 ($P_{ET}CO_2$, $P_{ET}O_2$) using a RespirAct^{TM} system, hyperoxia is administered without accompanying hypocapnia, to determine the independent effect of hyperoxia on physiology.

Aim: To assess the physiological assumptions made in hyperoxia-based calibrated BOLD. Here, we measure the effect of hyperoxia on (1) cerebral blood flow (CBF), as measured with Phase-Contrast Magnetic Resonance Angiography (PC-MRA), (2) arterial Cerebral Blood Volume (aCBV), as measured with LL-FAIR ASL and (3) neuronal activity, as measured from the oscillatory power measured with MEG.

Method: All experiments were approved by the local ethics committee and subjects gave informed written consent. MR data for experiment (1) and (2) were acquired using a Philips Achieva 7.0 T system with head volume transmit coil and 32-channel SENSE receive coil. MEG data for experiment (3) were acquired using the 3rd order gradiometer configuration of a 275-channel CTF MEG system at a 600Hz sampling frequency. For all experiments $P_{ET}CO_2$ and $P_{ET}O_2$ were independently controlled using a feed-forward, low gas-flow system (RespirAct^{TM,} Thornhill Research Inc., Toronto, Canada). *Experiment 1*: 5 healthy subjects (24-28 yrs) participated. The gas challenge consisted of 5 min of isocapnic hyperoxia ($P_{ET}O_2$ = 500 mmHg), followed by 5 min of normoxia ($P_{ET}O_2$ = 110 mmHg, subject specific $P_{ET}CO_2$), 10 min total duration. Sagittal and coronal 2D PC-MRA data (2 slices, thickness = 50mm, TR/TE = 14/7.4 ms, FA = 25°, FOV = 280x125 mm^2, SENSE 3) were acquired to visualise the location of the internal carotid arteries (ICA). PC-velocity measurements (TR/TE = 14/7.4 ms, FA = 25°, FOV = 280x125 mm^2, 0.75x0.75x6 mm^3, SENSE 3, scan duration = 1 min 25 secs for 2 averages) were acquired during the gas challenge on a 6 mm axial slice perpendicular to the ICA's. PC-MRA was VCG gated with 16-25 phases (dependent on heart rate) per RR period (trigger delay =40msec to capture systole only and minimise scan duration). V_{ENC} = 100 cm/s for normoxic, hyperoxic and hypercapnic conditions. Mean velocity, vessel area, and mean blood flow (MBF, ml/min) in the ICA were calculated using Q-flow analysis software (Philips). *Experiment 2:* 6 subjects (22-48 yrs) participated. aCBV was measured using LL-FAIR ASL [8] (TI/ΔTI/TR = 150/100/3000 ms, 21 phases, FA = 45°, single slice EPI, 2x2x3 mm^3 TE = 16 ms). Inversion recovery EPI images were acquired with 10 inversion times and fitted for T_1 to form a grey matter (GM) mask. The mean grey matter aCBV was calculated using a kinetic model for normoxia and hyperoxia [9]. The gas challenge consisted of 1 min of baseline followed by 2 min of hyperoxia ($P_{ET}O_2$ = 500 mmHg) and 1 min of baseline. *Experiment 3:* 9 subjects (23 – 30 yrs) participated. MEG data were recorded during the gas challenge which comprised of an initial 2 min period of baseline, followed by 2 cycles of 5 min of hyperoxia ($P_{ET}O_2$ = 500mmHg) separated by 4 min of baseline, total duration 21 min. MEG data were analysed across three brain regions (medial frontal, visual and right motor cortices). Neural oscillatory power was measured for the 21 minute experiment in 17 frequency bands, ranging from 1-80 Hz [2]. A Hilbert enveloped was derived for each frequency band and averaged across the normoxic and hyperoxic periods, yielding two spectra.

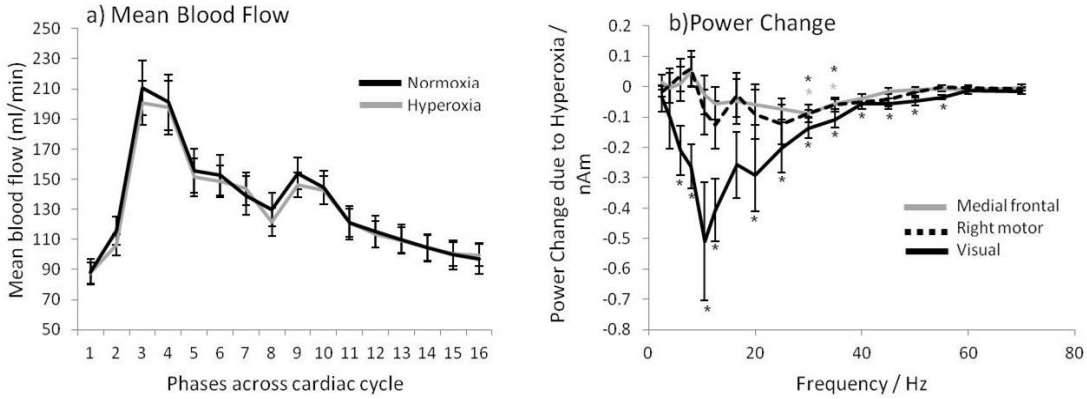

Figure 1A) Effects of hyperoxia on MBF in a representative subject. B) Power change due to hyperoxia as a function of frequency band for three locations. indicates p <0.05*

Results: $P_{ET}O_2$ increased to 473 ± 10 mmHg during hyperoxia (average ± standard error across subjects and experiments), while $P_{ET}CO_2$ varied by < 1 mmHg. *Experiment 1* A small but non-significant decrease in MBF averaged over the cardiac cycle was observed between normoxia (179 ± 14 ml/min) and hyperoxia (170 ± 13 ml/min) (Wilcoxon signed-rank test, p=0.92). *Experiment 2:* The mean grey matter aCBV data was 1.30 ± 0.37 % during normoxia and 1.25 ± 0.26 % during hyperoxia, this reduction was not significant (Wilcoxon signed-rank test, p=0.46). *Experiment 3:* In the visual cortex, a reduction in oscillatory power in response to hyperoxia was observed across all frequency bands which was significant (p< 0.05) in the 5-80 Hz range (Fig 1b).Changes were not significant in the right motor cortex and medial frontal area.

Conclusions: No significant change in CBF or aCBV was seen in response to hyperoxia, in agreement with a recent ASL study [10]. These results suggest that previous reports of hyperoxia-induced reduction in CBF [5,6,7] may have been influenced by the confounding effect of hypocapnia. A small focal reduction (<5%) in measured neural oscillatory power (5-80Hz) was observed in response to hyperoxia, which can be contrasted with a larger (~15%) global reduction observed on hypercapnia [2]. Hyperoxia is thus unlikely to have a significant effect on neuronal activity. Together, these haemodynamic and oscillatory findings support the physiological assumption that hyperoxia does not change neural activity, and that hyperoxia provides a reliable stimulus for calibrated BOLD.

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