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The effect of isocapnic hyperoxia on neurophysiology as measured with MRI and MEG

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ABSTRACT

The physiological effect of hyperoxia has been poorly characterize d, with studies reporting conflicting results on the role of hyperoxia as a vasoconstrictor. It is not clear whether hyperoxia is the primary contributor to vasoconstriction or whether induced changes in CO_2 that commonly accompany hyperoxia are a factor. As calibrated BOLD fMRI based on hyperoxia becomes more widely used, it is essential to understand the effects of oxygen on resting cerebral physiology. This study used a RespirAct™ system to deliver a repeatable isocapnic hyperoxia stimulus to investigate the independent effect of O_2 on cerebral physiology, removing any potential confounds related to altered CO_2. T_1-independent Phase Contrast MRI was used to demonstrate that isocapnic hyperoxia has no significant effect on carotid blood flow (normoxia 201 ± 11 ml/min, −0.3% ± 0.8% change during hyperoxia, $p = 0.8$), while Look Locker ASL was used to demonstrate that there is no significant change in arterial cerebral blood volume (normoxia 1.3% ± 0.4%, −0.5 ± 5% change during hyperoxia). These are in contrast to significant changes in carotid blood flow observed for hypercapnia (6.8% ± 1.5%/mm Hg CO_2). In addition, magnetoencephalography provided a method to monitor the effect of isocapnic hyperoxia on neuronal oscillatory power. In response to hyperoxia, a significant focal decrease in oscillatory power was observed across the alpha, beta and low gamma bands in the occipital lobe, compared to a more global significant decrease on hypercapnia. This work suggests that isocapnic hyperoxia provides a more reliable stimulus than hypercapnia for calibrated BOLD, and that previous reports of vasoconstriction during hyperoxia probably reflect the effects of hyperoxia-induced changes in CO_2. However, hyperoxia does induce changes in oscillatory power consistent with an increase in vigilance, but these changes are smaller than those observed under hypercapnia. The effect of this change in neural activity on calibrated BOLD using hyperoxia or combined hyperoxia and hypercapnia needs further investigation.

Introduction

Hyperoxia (raising the inspired fraction of oxygen (F_iO_2) above normal physiological levels (0.21)), is increasingly being used to provide exogenous contrast in functional magnetic resonance imaging (fMRI), primarily to provide a method of calibrating the blood oxygenation level dependent (BOLD) effect, but also to study venous blood oxygenation and venous blood volume (Blockley et al., 2012; Kwong et al., 1995; Rostrup et al., 1995; Bulte et al., 2007a, 2007b; Chiarelli et al., 2007a, 2007b; Driver et al., 2012, 2013). Hyperoxia increases arterial oxygen content (mostly through an increase in O_2 dissolved in blood plasma), thus increasing venous oxygen saturation, and hence decreasing the concentration of deoxyhemoglobin in capillaries and veins (Rostrup et al., 1995). This leads to an increase in the transverse relaxation time (T_2^*) of blood in vessels and the surrounding tissue, and thus a global increase in the BOLD-MRI signal (Losert et al., 2002; Ogawa and Lee, 1990).

Calibrated fMRI provides a non-invasive method of quantifying the fractional change in cerebral metabolic rate of oxygen ($CMRO_2$) consumption giving rise to a BOLD signal change during an fMRI experiment (Kastrup et al., 2002; Chiarelli et al., 2007a; Stefanovic et al., 2005; Uludag et al., 2004; Mohtasib et al., 2012; Davis et al., 1998). Hyperoxia has been suggested as an alternative to the more common hypercapnia-based BOLD calibration (Chiarelli et al., 2007b; Driver et al., 2012), providing the advantages of a more precise estimate of $CMRO_2$ and a more tolerable stimulus which can be applied for longer periods. Furthermore, hypercapnia-based BOLD calibration is likely to be compromised by the known change in electrophysiological activity with hypercapnic stimuli, and the impact this may have on $CMRO_2$ (Jones et al., 2005; Hall et al., 2011; Xu et al., 2011; Zappe et al., 2008; Thesen et al., 2012), although such a reduction in $CMRO_2$ is contested (Chen and Pike, 2010). To date, there remains some doubt as to the effect of hyperoxia on tissue blood flow and neuronal activity, and any such changes would complicate or undermine the use of hyperoxia-based BOLD calibration. More recently, a combined method of hyperoxia–hypercapnia BOLD calibration has been proposed (Bulte et al., 2012; Gauthier and Hoge, 2012), with the potential to offer a

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clinically viable alternative to positron emission tomography (PET) for quantification of baseline $CMRO_2$. However, this will combine the potential pitfalls associated with the separate delivery of hyperoxia and hypercapnia, and so further emphasises the need to fully understand the accuracy of each of these methods.

Reports in the literature as to the effect of hyperoxia on tissue blood flow are contradictory (Kety and Schmidt, 1948; Watson et al., 2000; Kolbitsch et al., 2002; Bulte et al., 2007b). Some previous studies may have been confounded by associated arterial hypocapnia, caused by the Haldane effect (a reduction in CO_2 carrying capacity of oxyhemoglobin during hyperoxia) (Becker et al., 1996; Loeppky et al., 1983). For example, Bulte et al. reported a reduction of approximately 4 mm Hg in $P_{ET}CO_2$ under 60% O_2 ((Kety and Schmidt, 1948; Watson et al., 2000; Kolbitsch et al., 2002; Bulte et al., 2007b). Since the vasculature is very sensitive to changes in blood levels of CO_2 (Bray, 1999), a relatively low level of concomitant hypocapnia, may significantly decrease blood flow. Therefore, to properly characterize the effect of hyperoxia, it is important to control or monitor any confounding changes in the level of CO_2. An additional complication is that the technique of Arterial Spin Labeling (ASL), which is frequently used to measure cerebral blood flow (CBF), is sensitive to tissue and blood longitudinal relaxation times (T_1). During hyperoxia, dissolved plasma oxygen shortens the T_1 of blood (Noseworthy et al., 1999; Tadamura et al., 1997) and tissue (O'Connor et al., 2007) which would lead to an under-estimation of CBF during hyperoxia if not properly accounted for when modeling the data.

The effect of hyperoxia on underlying neuronal activity can also be studied using electrophysiology. Using electroencephalography (EEG) to assess the effect of 35% O_2 on cognitive performance and brain activity, Seo et al. (2007b) found a reduction in beta and gamma power in the left and right hemispheres, an increase in delta power in the left and right hemispheres, and a reduction in alpha power in the left side of the brain. However, others (Lindauer et al., 2003; Smith and Strawbridge, 1974; Kaskinoro et al., 2010) have found no significant effect of a change in blood oxygenation level on electrophysiology signals. These studies have either employed scalp level electric field measures (EEG) or very focal invasive electrode recordings (rat whisker studies (Lindauer et al., 2003)). Magnetoencephalography (MEG) provides a non-invasive method of spatially resolving the electrophysiological effects of hyperoxia across cortical gray matter.

The aim of this study was to assess changes in blood flow and localized neuronal activity in response to isocapnic hyperoxia. We used a RespirAct™ (Thornhill Research Inc., Toronto, Canada) system to provide independent control of end-tidal levels of O_2 ($P_{ET}O_2$) and CO_2 ($P_{ET}CO_2$). MR measurements were performed at ultra-high field (7 T) to provide increased signal-to-noise ratio (SNR), and lengthened T_1 relaxation times, increasing the contrast-to-noise ratio (CNR) in ASL (Gardener et al., 2009). ASL measurements were used to quantify arterial cerebral blood volume (aCBV), rather than CBF, as aCBV is thought to drive the CBF and BOLD signal changes (Brookes et al., 2007; Zheng et al., 2002) and aCBV weighted ASL has greater sensitivity than CBF weighted ASL measures (Brookes et al., 2007; Zheng et al., 2002). Phase contrast (PC) MRI was used as a T_1 independent measure of blood flow. Finally, MEG was used to monitor the effects of hyperoxia on electrophysiological brain activity.

Methods

This study comprised two MR sessions (Experiments 1 and 2) and one MEG session (Experiment 3). The study was approved by the University of Nottingham Medical School ethics committee and subjects gave prior informed written consent. Six subjects (aged 24–28 years, 4 female) participated in Experiment 1, 7 subjects (age 24–48 years, 3 female,) participated in Experiment 2, and 9 subjects (age range 23–30 years, 4 female) participated in Experiment 3. MR scanning was performed using a Philips Achieva 7.0 T system with head volume transmit and 32-channel SENSE receive coil with foam padding used to reduce head motion. MEG recordings were made using a 275-channel axial gradiometer (CTF) MEG system (MISL, Port Coquitlam, BC, Canada) at a rate of 600 Hz, with a 150 Hz anti-aliasing hardware filter and with a synthetic third order gradiometer interference suppression system.

A feed-forward, low gas flow system (RespirAct™, Thornhill Research Inc., Toronto, Canada) and a sequential gas delivery (SGD) breathing circuit were used to target end-tidal PCO_2 ($P_{ET}CO_2$) and PO_2 ($P_{ET}O_2$) independently (Slessarev et al., 2007), and maintain a constant normoxic baseline where necessary. Source gases used by the system were 100% O_2, medical air and two blends of O_2, CO_2 and N_2 gas each containing a minimum of 10% O_2 for safety purposes. Using the approach of Slessarev et al. (2007), the RespirAct™ determines the required flow of these source gases, to target pre-determined $P_{ET}CO_2$ and $P_{ET}O_2$ values. Prior to MRI or MEG measurement, the subject sat upright on the scanner bed while baseline metabolic values were estimated and targeted. While lying supine in the scanner, the subject received medical air via the RespirAct™ until the respiratory challenge commenced.

Experiment 1: Phase contrast MRI flow measurement under hyperoxia and hypercapnia

The experiment involved 1 minute of normoxic baseline followed by 5 minutes of isocapnic hyperoxia ($P_{ET}O_2$ targeted at 500 mm Hg, equivalent to $F_iO_2 = 0.6$, at subject's resting $P_{ET}CO_2$, included as a positive control), and then 5 minutes of normoxic baseline. This was then followed by 2 cycles of 2 minutes of hypercapnia (subject's resting $P_{ET}O_2$, $P_{ET}CO_2$ targeted at baseline + 8 mm Hg), separated by 2 minutes of baseline, followed by 1 minute of baseline (Fig. 1A). The total duration of the respiratory challenge was 20 minutes, including transitions between the different blood gas levels. All hyperoxia transitions consisted of a graded increase/decrease in target $PETO_2$ (between subject specific baseline and 500 mm Hg across 1 minute) in order to minimize a sudden influx of gas, as is common with a square-wave transition. This minimizes discrepancies between targeted and actual $PETO_2$, allowing a steady-state to be reached near instantaneously.

Sagittal and coronal 2D PC-MRI data sets (2 slices of thickness 30 mm, TR/TE = 14/7.6 ms, FA = 20°, FOV = 230 × 230 mm^2, SENSE 2, v_{ENC} = 30 cm/s scan duration = 47 s for number of signal averages (NSA) 4) were acquired prior to the respiratory challenge to locate the left and right internal carotid arteries (ICA) and other major vessels in the neck. Blood flow in each ICA was measured using a vectorcardiogram (VCG) gated, 2D PC-MRI (TR/TE = 15/6.5 ms, FA = 25°, FOV = 280 × 77 mm^2, 0.75 × 0.75 × 6 mm^3 reconstructed, SENSE 4, v_{ENC} = 0 and 100 cm/s, scan duration = 1 min 25 s for 2 averages) on a single slice perpendicular to the targeted ICA with 16–25 phases (dependent on subject heart rate). The measurement plane was positioned through the C1 segment of the spinal cord, where the left and right ICAs were approximately parallel (Fig. 2A). PC-MRI data were collected throughout the 20 minute respiratory challenge with 4 repeats collected at normoxia, hyperoxia, and hypercapnia.

PC-MRI flow data were analyzed using QFlow software (Philips, Best, the Netherlands). Regions of interest (ROIs) were drawn manually around the lumen of the carotid arteries on each phase contrast image (Fig. 2B); contour detection software was used to improve the ROI accuracy. The mean signal intensity within each ROI reflected the flow velocity in the vessel (cm/s) for each cardiac phase. The cross-sectional area of each vessel lumen was multiplied by the velocity, to compute, for each cardiac phase, the carotid artery blood flow in ml/min.

The flux data were then averaged across left and right ICAs, and repeated measurements, to give an average carotid artery flux waveform at normoxia, hyperoxia and hypercapnia. These data were then averaged across all subjects to give a mean response across cardiac cycle, and across all phases of the cardiac cycle to provide a single value from which to estimate mean blood flow (MBF) at normoxia, hyperoxia and hypercapnia. The change in MBF induced by hyperoxia and