Assessment of the linearity of the R$_2^*$ dependence on blood oxygenation and measurement of venous CBV using hyperoxia at 7T

Paula L. Croal$^1$, Ian D. Driver$^1$, Emma L. Hall$^1$, Susan T. Francis$^1$, and Penny A. Gowland$^1$

$^1$Sir Peter Mansfield MR Centre, University of Nottingham, Nottingham, Nottinghamshire, United Kingdom

Introduction: Hyperoxia is an isometabolic perturbation that can be used to probe the haemodynamic properties of the BOLD response [1]. Yablonskiy et al. proposed a model suggesting that R$_2^*$ is linearly dependent on blood oxygenation [2]. The linearity of R$_2^*$ with blood oxygenation is a critical assumption in most models of the BOLD signal, and in the measurement of venous cerebral blood volume (vCBV) using hyperoxia. When modulating end tidal oxygen levels ($P_{ETO_2}$) to induce hyperoxia it is essential to maintain a constant $P_{ETCO_2}$, since hypercapnia causes changes in CBF. Aim: To test the linearity of R$_2^*$ in grey matter (GM) across a range of precisely targeted $P_{ETO_2}$ levels, whilst maintaining constant $P_{ETCO_2}$.

Method: The study was performed on 6 healthy subjects (four female, 24 years). Data acquisition: Scanning was performed on a Philips Achieva 7.0T, with head volume transmit and 32-ch SENSE receive coil. Axial images were acquired using a double-echo GE-EPI sequence (SENSE = 2.5, $TE = 16/47$ ms, $TR = 3$s, 192x192 x 15mm FOV, 2x2x3mm$^3$ voxel resolution, 5 slices). Inversion recovery EPI images were acquired using the same geometry, with data collected at 10 TIs (100 – 2500 ms) and $T_1$ maps were formed to create a GM mask. Paradigm: The gas challenge, was administered by a feed-forward, low gas-flow system (RespirAct$^\text{TM}$, Thornhill Research Inc., Toronto, Canada). One minute of baseline normoxia (subject specific $P_{ETO_2}$) was followed by a 4 minute linear increase in $P_{ETO_2}$ to 500 mmHg and a 4 minute linear decrease to normoxia (8mmHg steps at each breath; Fig 1A), and then one minute of normoxia. $P_{ETCO_2}$ was targeted at a subject specific baseline throughout. Data analysis: Motion correction was applied to the first echo using FSL (FMrib, Oxford, UK), and the resulting transforms applied to the second echo. Breath-by-breath $P_{ETO_2}$ was re-sampled and manually aligned with $R_2^*$ time course averaged over GM voxels, and $P_{ETO_2}$ converted to blood oxygenation ($Y$) [1]. Linear regression was performed between average GM $\Delta R_2^*$ and $Y$, and the gradient of this line was used to estimate vCBV [2]. The analysis was also performed on a voxel-by-voxel basis for GM.

Results: All subjects' $P_{ETO_2}$ closely matched the targeted hyperoxic paradigm (Fig 1A) with an average hyperoxic peak of 488 ± 14 mmHg across subjects, while $P_{ETCO_2}$ varied by < 1mmHg. The $R_2^*$ time course closely followed the $P_{ETO_2}$ time course. Average GM $R_2^*$ at normoxic baseline was 35.8±0.9 s$^{-1}$. A significant negative correlation was observed between $P_{ETO_2}$ and $R_2^*$ in all subjects (Pearson product-moment correlation coefficient, 0.56$< r < 0.83$, $p< 0.001$ in all cases) (Fig. 1B). The gradient, representing the change in $R_2^*$ per mmHg of $P_{ETO_2}$ was 2.7 ± 0.4x10$^{-3}$ s$^{-1}$mmHg$^{-1}$. vCBV was calculated to be 1.97 ± 0.06 % (mode = 0.83%), average across subjects. Figure 1C shows a map of vCBV in a representative subject. Figure 1D shows the distribution of vCBV across voxels across all subjects.

Discussion: This study presents the effect of graded hyperoxia on GM $R_2^*$, whilst removing any confounds induced by fluctuations in $P_{ETCO_2}$. Baseline $R_2^*$ values were consistent with previous studies at 7T [4]. Mean GM vCBV is somewhat higher than results previously reported at 3T (1.75 %) possibly due to the use of GESSE in that sequence which may have suppressed some signal from flowing blood in large veins [5]. The advantage of this method over previous methods of measuring vCBV using hyperoxia [6] or contrast agent methods is that it does not assume that the relaxivity of the oxygen is the same in the vein and the tissue, and does not require the selection of blood-filled voxels for normalisation.