The Effect of Dissolved Oxygen on Relaxation Rates of Blood Plasma

Yuhan Ma[1], Avery J.L. Berman[1], and G. Bruce Pike[1,2]

[1]*McConnell Brain Imaging Center, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada,* [2]*Hotchkiss Brain Institute and Department of Radiology, University of Calgary, Calgary, Alberta, Canada*

Introduction: The calibrated BOLD method is a quantitative MRI technique used to measure the cerebral metabolic rate of oxygen ($CMRO_2$) — an important index of neuroenergetics and biomarker of brain tissue viability (1, 2). The calibrated BOLD method has traditionally been performed by inducing elevated BOLD signals by mixed gas inhalation to achieve conditions of hypercapnia and/or hyperoxia (3, 4). During a hyperoxia calibration, extra oxygen dissolves in arterial blood plasma because hemoglobin is fully oxygenated. Excess oxygen from arterial plasma in turn reduces the concentration of deoxyhemoglobin (dHb) in venous and capillary blood to produce a positive BOLD response. Although the effect of dissolved oxygen in arterial blood plasma on the BOLD signal is generally ignored with arterial oxygen tension < 350 mmHg (5), a recent theoretical study by Schwarzbauer and Deichmann has suggested that excess oxygen dissolved in arterial blood plasma can produce pronounced intravascular and extravascular BOLD signal changes, thereby complicating the interpretation of the measured hyperoxia response and confounding its use in calibrated BOLD based measurement of $CMRO_2$ (6). Due to the paucity of experimental data on this subject, this study intends to resolve the issue by experimentally examining the effect of dissolved oxygen in bovine plasma. Specifically, R_1, R_2 and R_2^* relaxation rates of bovine plasma were measured under various partial pressures of oxygen.

Methods: Normal bovine blood plasma (GeneTex, Inc) was used to mimic human blood plasma because bovine plasma's macromolecular compositions are similar to that of human plasma's. Plasma samples with oxygen partial pressures (pO_2) ranging from 100 – 600 mmHg were prepared by bubbling pure oxygen into the samples. Oxygen partial pressures were measured using a dissolved oxygen meter (Orion^{TM}Star^{TM}, Thermo Scientific). Plasma samples were held in 15-ml centrifuge tubes, which were embedded in a watertight container filled with 20 μM $MnCl_2$ and 48 mM NaCl solutions. All experiments were performed in a Siemens Tim Trio 3T scanner with a 32-channel RF receiver coil. A single 1 cm thick slice with a resolution of 0.5×0.5×10 mm^3 was acquired. T_1 was measured using an inversion recovery sequence with six inversion times at TI = 30, 530, 1200, 2000, 3800, 5300 ms and TR = 6 s. T_2 was measured using a spin-echo sequence with 32 echo times (echo spacing 15 ms). T_2^* was measured using a gradient echo sequence with 32 echoes ranging from 10 to 560 ms. Prior to each T_2^* measurement, localized shimming (FASTESTMAP, Siemens) was performed to minimize the macroscopic static field inhomogeneities that can shorten T_2^* (7). Relaxation rates (R_1, R_2 and R_2^*) of plasma under different oxygen partial pressures were fitted using custom Matlab (Mathworks, Inc) scripts.

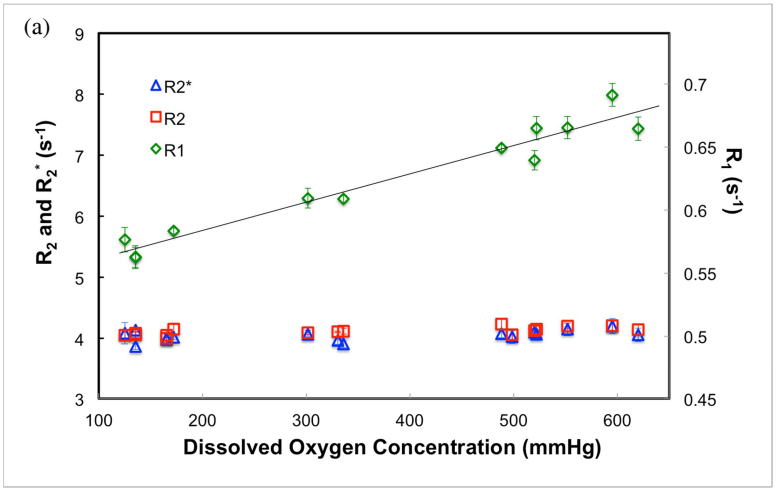

Figure 1 (a) Relaxation rates of bovine plasma versus various dissolved oxygen concentrations. R_1 increases linearly with pO_2 with $R^2 = 0.95$. (b) A comparison of bovine plasma R_2 and R_2^* at pO_2=135 mmHg and 600 mmHg yield no statistically significant change in relaxation rates ($p = 0.06$ for R_2, $p = 0.76$ for R_2^*).

Results: As shown in Fig. 1a, the R_1 of bovine plasma linearly increases with oxygen concentration. The longitudinal relaxivity of dissolved oxygen in bovine plasma was found to be $R_{1,O2} = 2.2 \pm 0.2 \times 10^{-4}\ s^{-1}mmHg^{-1}$. As pO_2 increased, R_2 and R_2^* did not show statistically significant changes (Fig. 1b), indicating that dissolved oxygen did not introduce significant microscopic field inhomogeneities. Additionally, measured R_2^* and R_2 values were nearly identical, verifying that the residual macroscopic field inhomogeneities were negligible using the FASTESTMAP shimming technique.

Discussions and Conclusions: These results are consistent with previous studies, where the enhancements of R_1 relaxation rates were reported in blood plasma and tissues to be due to the paramagnetic effect of oxygen molecules (8, 9). The range of pO_2 over which our measurements were taken cover the typical range of arterial pO_2 found in subjects during the hyperoxia calibration method (3). In blood plasma under this range of pO_2, unlike hemoglobin-containing whole blood, excess oxygen has minimal effect on R_2 and R_2^* relaxation rates. Similar studies have shown that dissolved oxygen in human tissues from inhalation of pure oxygen did not induce changes in R_2 (9). As a result, dissolved oxygen in arterial blood plasma should not induce significant BOLD signal change through T_2 and T_2^* effects, as previously predicted (6). This finding supports a recent theoretical study, which predicted that dissolved oxygen has minimal effect on the susceptibility of blood plasma during hyperoxia (10). The enhancement of R_1 in arterial blood plasma during hyperoxia may introduce additional intravascular and extravascular BOLD signal contrast depending on sequence parameters, which should be investigated in the future. Overall, this study verifies that, under hyperoxia, BOLD signal contrast arises from changes in the concentration of dHb in venous and capillary blood - the fundamental basis of the calibrated BOLD method - and not dissolved oxygen in arteries.

Reference [1] Davis, T. L., et al. PNAS USA 95: 1834 (1998) [2] Hoge, R. D. and Pike, G. B. J Chem Neuroanat 22: 43 (2001) [3] Chiarelli, P. A., et al. Neuroimage 37: 808 (2007) [4] Mark, C. I., et al. Neuroimage 54: 1102 (2011) [5] Berkowitz, B. A. MRM 15: 123 (1997) [6] Schwarzbauer, C. and Deichmann, R. Neuroimage 59: 2401 (2012) [7] Gruetter, R. and Tkac, I. MRM 43: 319 (2000) [8] Young, I. R., et al. J Comput Tomogr 5: 543 (1981) [9] Tadamura, E., et al. JMRI 7: 220 (1997) [10] Berman, A., et al. Proc. of ISMRM (2013)