The impact of dissolved oxygen in blood on hyperoxia-based BOLD calibration

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Introduction – In quantitative fMRI studies of brain physiology, methods involving respiratory challenges are commonly implemented in order to elicit a BOLD and/or CBF signal change for calibration. The inhalation of elevated levels of O_2 (hyperoxia) is one such technique. Under hyperoxia, the partial pressure of O_2 in blood is high enough such that nearly all arterial hemoglobin (Hb) is in the oxygenated state and an excess of O_2 molecules end up dissolved in arterial blood[1]. Assuming the cerebral metabolic rate of O_2 remains constant during hyperoxia, the excess O_2 in arterial blood that does not get consumed ends up bound to Hb in veins, leading to a reduction of the venous concentration of deoxygenated-Hb (dHb) compared to normoxia.

Until recently, the model used to describe hyperoxic-induced signal changes was one where the reduction in paramagnetic dHb led to an increase in BOLD signal compared to baseline for veins and capillaries but no significant change for arteries. However, this model was challenged in a recent paper by Schwarzbauer and Deichmann (SD) who theoretically predicted that paramagnetic O_2 dissolved in blood would significantly contribute to the magnetic susceptibility difference between arterial blood and the surrounding tissue when concentrations of dissolved O_2 in blood were sufficiently high, such as during hyperoxia[2]. Based on this, they predicted, using simulations, that during hyperoxia, signal change in arteries could be substantial and even comparable to venous BOLD contrast. The implications of these findings for calibrated fMRI studies using hyperoxia are profound and have led us to re-examine the model of the susceptibilities of blood and tissue proposed by SD.

Theory – For a mixture of substances in solution, such as in blood, the net volume magnetic susceptibility of the solution, $\chi_{V,net}$, is given by the weighted sum of the individual volume susceptibilities: $\chi_{V,net} = \sum \alpha_i \cdot \chi_{V,i}$. The weighting factors, α_i, are the volume fractions of the substances in solution. In the SD paper, the net susceptibility of blood, $\chi_{V,b}$, was divided into contributions from O_2, with a volume fraction α_{O_2}, and from red blood cells and plasma, with a volume fraction $1 - \alpha_{O_2}$. α_{O_2} was obtained from the plasmatic component of the blood O_2 content, given by $\varepsilon \cdot P_{O_2}$, where $\varepsilon = 3.1\times10^{-5}$ mL O_2/mL blood/mm Hg[1], is the solubility of O_2 in blood, and P_{O_2} is the partial pressure of O_2 in blood. However, the volume of O_2 in this particular expression is the volume the dissolved O_2 would occupy if it were released into the gaseous state at standard temperature and pressure (STP), it is *not* the physical volume occupied by dissolved O_2 in blood. In fact, when O_2 dissolves in a liquid such as blood or water, the volume occupied by the O_2 in solution is orders of magnitude less than the volume occupied by the same number of moles in the gaseous state at STP. Therefore, SD's formulation severely overestimated α_{O_2}. Similarly, the susceptibility of tissue was divided into a baseline tissue component and a dissolved O_2 component with α_{O_2} again given by the product of the solubility of O_2 in blood and the P_{O_2} in tissue.

To compute the effect of dissolved O_2 on $\chi_{V,b}$, we first propose to simplify the problem by considering the O_2 dissolved in each water compartment of blood; specifically, the water in plasma and in red blood cells. The volume fractions can then be determined using data that is readily available, specifically, the mole fraction solubilities of O_2 in water, $\bar{n}_{O_2:H_2O}$, as well as the partial molar volume of O_2 dissolved in water, $\bar{v}_{O_2:H_2O}$. For the range of P_{O_2} encountered under normoxia and hyperoxia, the dissolved O_2-water solution is very dilute, therefore, the partial molar volume of water can be approximated by the molar volume of water, v_{H_2O}. Using the terms listed above to compute α_{O_2}, we finally determine $\chi_{V,b}$ using a modified form of the susceptibility of blood provided by Spees *et al.*[3] whereby every appearance of the susceptibility of water, χ_{V,H_2O}, is replaced by $(1 - \alpha_{O_2}) \cdot \chi_{V,H_2O} + \alpha_{O_2} \cdot \chi_{V,O_2}$. For the susceptibility of tissue, we use the same model as SD but with α_{O_2} in tissue computed using our formulation assuming tissue has the same solubility to O_2 as water.

Results – While the literature on experimental studies of the effect of dissolved O_2 in either water or blood on the susceptibility of the solution is lacking, a related experiment that measured the effect of dissolved O_2 in benzene was used to validate our formulation[4]. Using mole fractions and partial molar volumes of O_2 in benzene instead of water, our model predicted $\chi_{V,net}$ to within -0.9% and -10% of the experimentally measured value at a P_{O_2} of 665 mm Hg using the ^{1}H and ^{13}C resonances of benzene, respectively. Given the good agreement between our formulation of the susceptibility and the measured values in benzene, one would expect similar results for dissolved O_2 in blood. Figure 1a shows the results of our formulation versus SD's formulation for the susceptibility of blood as a function of P_{O_2}. Figure 1b then shows how these susceptibilities correspond to the susceptibility differences between blood and tissue along the vascular tree during hyperoxia and normoxia using the same physiological parameters as SD[2].

Conclusion – Although the susceptibility of blood is still affected by the paramagnetic contribution from dissolved O_2 at elevated P_{O_2}, the effect is far smaller according to our formulation than was originally suggested by SD. This results in a negligible change in the arterial tissue-blood $\Delta\chi_V$ going from normoxia to hyperoxia - unlike SD's result - and a change in the venous $\Delta\chi_V$ similar to that of SD's. This means, therefore, that signal contrast will indeed be isolated to the venous and capillary sections of the cerebrovasculature during hyperoxia due to the decreased concentration of dHb alone - as was originally assumed. Furthermore, since the biophysical model of the BOLD signal used in calibration is dependent on contrast arising from dHb[5], the model is still valid when hyperoxic calibration is used. Further experiments and/or simulations should be performed to verify these results.

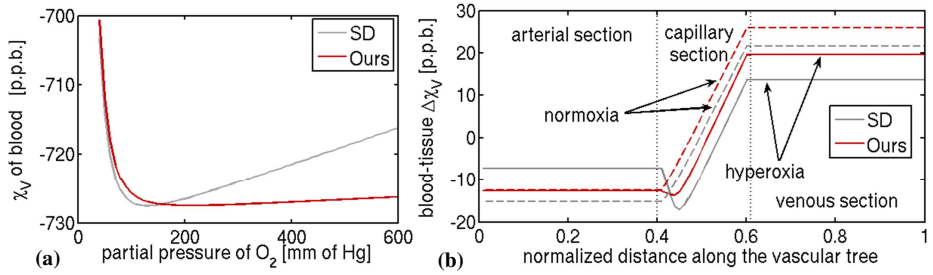

Figure 1: The volume magnetic susceptibility of blood as a function of P_{O_2}(a) and the resulting susceptibility difference between blood and tissue along the vascular tree (b). Both figures show comparisons of SD's formulation (grey) with our formulation (red). In (b), $\Delta\chi_V$ is shown for both formulations under hyperoxia (solid lines) and normoxia (dashed lines). In (b), the oxygen extraction fraction was 0.35, hematocrit was 0.44, and arterial pO_2 was 550 mm Hg for hyperoxia and 110 mm Hg for normoxia.

References – [1] Severinghaus, J. Appl. Physiol. 46:599 (1979). [2] Schwarzbauer and Deichmann, Neuroimage 59:2401 (2012). [3] Spees *et al.*, MRM 45:533 (2001). [4] Delpuech *et al.*, JMR 36:173 (1979). [5] Hoge *et al.*, MRM 42:849 (1999).