What is the best way to use hyperoxia to measure venous cerebral blood volume?

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Introduction: Hyperoxia has been proposed as a method to measure venous cerebral blood volume (CBVv), based on the BOLD response due to increased venous haemoglobin saturation (1). In analogy with T_1-based contrast agent studies for measuring total CBV, the measured BOLD signals are normalized by the signal from a 100% CBV voxel located in a large vein. This assumes that the signals measured in both cases are dominated by intravascular signal change. However, we know that the tissue signal has a significant extravascular component that makes up about 70% of the total signal at 3.0 T. We simulated the effect of hyperoxia using a detailed model of the BOLD signal (2) to test the sensitivity of the CBVv determination to physiological variability across subjects due to haematocrit and resting oxygen extraction fraction, variables that typically are unknown. The surprising result was that the raw BOLD response to hyperoxia—*before* normalization—is less sensitive to intersubject physiological variability, leading us to propose a new method for estimating CBVv.

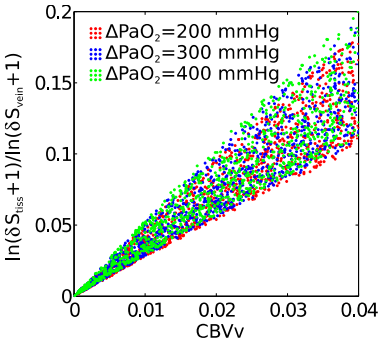

Fig. 1 – Original method Eq. [1]: Large uncertainty in the relationship between CBVv and the measurement due to physiological variability.

Methods and Results: The detailed BOLD signal model (2) includes both intra- and extravascular signal contributions from three vascular compartments; arteries, capillaries and veins. It also enables underlying physiological parameters such as Hct and OEF to be varied. In this analysis, haematocrit (Hct) and oxygen extraction fraction (OEF) were allowed to vary between 0.37-0.50 and 0.35-0.55, respectively. The signal change ($\delta S=\Delta S/S_0$) was simulated for the tissue (*tiss*) and the vein (*vein*) for a fixed change in arterial partial pressure of oxygen (ΔPaO_2) over a range of tissue CBVv fractions (0-0.1). In order to sample many combinations of Hct, OEF and CBVv, random combinations of these parameters were selected from their ranges and values of δS_{tiss} and δS_{vein} generated. One thousand paired values of δS were produced, and the possible measured signals were plotted against true CBVv to assess the scatter expected due to variations in Hct and OEF. For the original method, CBVv is calculated using Eq. [1] where h=(1-Hct)/(1-r Hct) accounts for differences in small vessel Hct (r=0.85) and ρ=1.04 g/ml is the density of brain tissue (1). Fig. 1 shows that the measured quantity exhibits substantial scatter relative to CBVv. In contrast to this method, we tested in a similar way the unnormalised BOLD response to hyperoxia, and found a much tighter relationship with CBVv in the presence of unknown variations in Hct and OEF (Fig.2). This suggests a new analysis approach that does not require a measurement of the venous signal change, δS_{vein}. CBVv is calculated (Eq. [2]) by multiplying δS_{tiss} by a scaling factor defined by the echo time, *TE*, ΔPaO_2, and 4 model parameters; *A*, *B*, *C* and *D*. Fitting Eq. [2] across a range of likely *TE* and ΔPaO_2 values yields A=27.0 ms, B=0.2, C=245.1 mmHg, and D=0.2 (fits are shown as dark lines in Fig. 2). We also examined the systematic error introduced if hyperoxia reduces CBF by 5%, creating an additional contribution to the local deoxyhemoglobin change. Fig. 3 shows that this significantly shifts and broadens the relationship between the measured signal and CBVv, and represents an important source of systematic error.

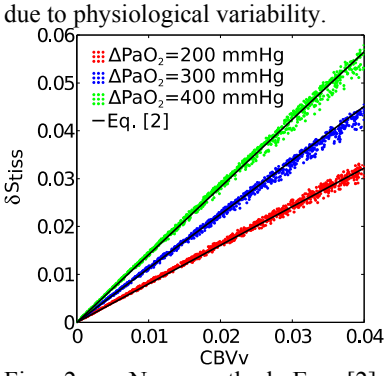

Fig. 2 – New method Eq. [2]: Hyperoxia-BOLD δS_{tiss} alone has a tighter relationship with CBVv.

$$CBVv = \frac{h}{\rho}\frac{\ln(\delta S_{tiss}+1)}{\ln(\delta S_{vein}+1)} \qquad [1]$$

$$CBVv = \left(\frac{A}{TE}+B\right)\left(\frac{C}{\Delta PaO_2}+D\right)\delta S_{tiss} \qquad [2]$$

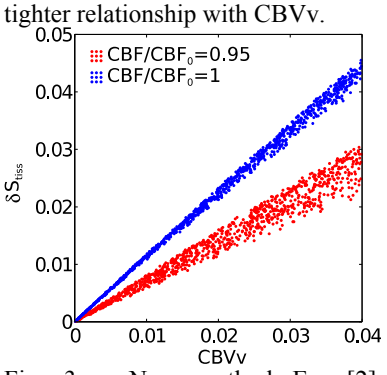

Fig. 3 – New method Eq. [2]: Changes in CBF due to hyperoxia increase uncertainty in the relationship of δS_{tiss} and CBVv.

Discussion: An ideal method for measuring venous CBV should produce a tight one-to-one relationship between the measured quantities and CBVv, regardless of differences in Hct and OEF across subjects. If these unknown variables broaden the distribution of possible measurement outcomes for a given CBVv increase, the uncertainty of the CBVv estimate grows. Fig. 1 shows that the original measurement technique (Eq. [1]) gives a large uncertainty in CBVv. However, by plotting δS_{tiss} alone (Fig. 2) a much lower uncertainty in the value of CBVv can be achieved. This perhaps paradoxical result can be explained by considering two elements of the signal change. Firstly, the change in extravascular R_2^* due to hyperoxia is proportional to CBVv and the change in deoxyhaemoglobin concentration (Δ[dHb]). Secondly, oxygen transport modelling reveals that Δ[dHb] caused by hyperoxia is almost independent of Hct and OEF. Hence changes in tissue signal with hyperoxia should be proportional to CBVv. However, during an uncontrolled hyperoxic respiratory challenge it is likely that CBF may be reduced (3), resulting in an altered relationship between δS_{tiss} and CBVv, and increased uncertainty (Fig. 3). A reduction in CBF causes oxygen extraction to increase and, unlike with hyperoxia, the resulting decrease in deoxyhaemoglobin concentration is dependent on baseline Hct and OEF. Because there is no simple correction without knowing Hct and OEF, it is important to prevent CBF from changing during the experiment. Fortunately techniques to produce tightly controlled respiratory challenges are now available, enabling the CBF reduction to be minimised (4). Finally, it is interesting to note that for TE=30 ms and ΔPaO_2=306 mmHg the percentage BOLD signal due to hyperoxia is numerically equal to the CBVv.

References: (1) Bulte *et al*., JMRI, 26:894 (2007), (2) Griffeth & Buxton, NI, 58:198 (2011), (3) Bulte *et al*., JCBFM, 27:69 (2007), (4) Prisman *et al*., JMRI, 27:185 (2008).