Analysis of calibrated BOLD based methods for quantifying the resting oxygen extraction fraction

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Introduction: Recently a new class of calibrated BOLD methods was introduced to quantitatively measure the resting oxygen extraction fraction (OEF)[1,2]. Such methods rely on two, or more, respiratory challenges using increased inspired carbon dioxide and/or oxygen to produce a BOLD response. A mathematical model of this response is used to estimate the resting OEF. However, to date the sensitivity of these methods to variations in haematocrit and cerebral blood volume, or to a breakdown of the physiological assumptions that underpin them, has not been performed. In this study we employed a detailed model of the BOLD signal to simulate these effects following earlier work[3].

$$\delta S_{hc} = M_{hc}\left(1 - f_{hc}^{\alpha-\beta}\right) \quad \text{Eq. [1]}$$

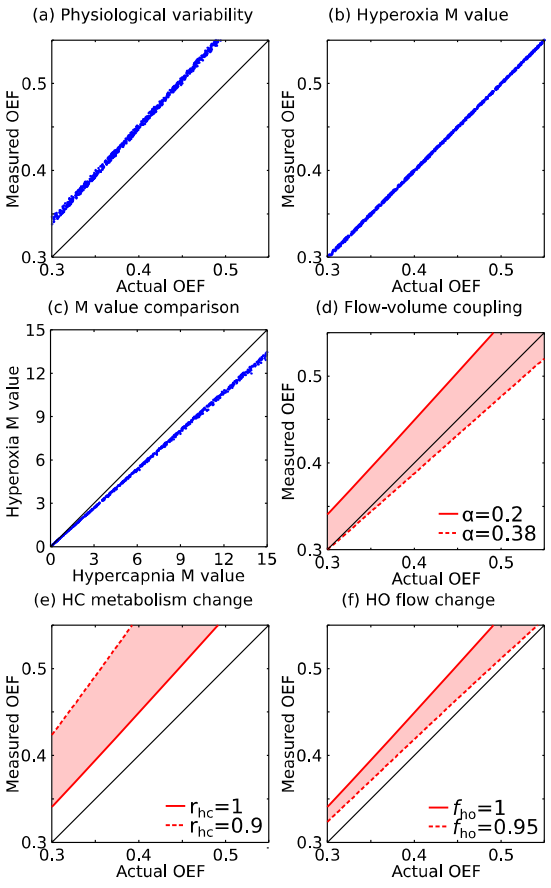
$$\delta S_{ho} = M_{ho}\left[1 - \left(1 + \frac{\Delta[dHb]}{[dHb]_0}\right)^{\beta}\right] \quad \text{Eq. [2]}$$

$$[dHb]_0 = [Hb](1 - SaO_2(1 - E_0)) \quad \text{Eq. [3]}$$

Theory: To briefly summarise, the BOLD scaling factor, M, is measured from a hypercapnia (hc) challenge[4] using measurements of the fractional BOLD signal change, δS, the normalised blood flow change, f (=F/F$_0$), and Eq. [1]. Eq. [2] can be used to measure M from a hyperoxia (ho) challenge[5]. However, by substituting M$_{hc}$ into Eq. [2] resting deoxyhaemoglobin concentration, [dHb]$_0$, can be measured. The decrease in [dHb] due to hyperoxia, Δ[dHb], is estimated from measurements of end-tidal PO_2. In turn Eq. [3] can be used to calculate the resting OEF, E$_0$, given information about arterial oxygen saturation, SaO_2, and total haemoglobin concentration, [Hb], which is related to haematocrit. However, these equations reflect the ideal experiment and several assumptions are made including that oxygen metabolism doesn't change during hypercapnia, blood flow does not change during hyperoxia and that flow-volume coupling is accurately described by the exponent α. We investigated the implications of a failure of these assumptions on this method.

Simulations and Results: The detailed BOLD signal model[6] includes both intra- and extravascular signal contributions from three vascular compartments; arteries, capillaries and veins. It also enables underlying physiological parameters such as [Hb], OEF and total cerebral blood volume (CBVt) to be varied. In this analysis, [Hb] and CBVt were allowed to vary between 12.3-16.7 $g_{Hb}dl^{-1}$ and 0-10%, respectively. The BOLD signal change to hypercapnia, δS$_{hc}$, and hyperoxia, δS$_{ho}$, were simulated over the physiological OEF range: E$_0$=0.3-0.55. To examine the effect of normal physiological variability many combinations (n=1000) of [Hb] and CBVt were randomly selected from within these ranges, and values of δS generated. Eqs. [1]-[3] were then used to simulate the OEF measurement. Fig. 1a plots the simulated measurement against the actual OEF, where the black line represents perfect agreement. Since a systematic offset was revealed, calculations were repeated using the simulated hyperoxia M value in Eq. [2] (a solution not available experimentally since *a priori* knowledge of OEF is required). Perfect agreement is revealed (Fig. 1b) leading to the observation that M$_{hc}$ and M$_{ho}$ are not equivalent (Fig. 1c). Physiological assumptions were examined by fixing [Hb]=14.7 $g_{Hb}dl^{-1}$ and CBVt=0.05. The results are plotted in Fig. 1d-f for the ideal experiment (solid red line) and for the assumption in question (dashed red line). Flow-volume coupling was examined by simulating changes in CBV using α=0.38, rather than the more standard α=0.2 (α=0.2 used throughout in Eq. [1]). Fig. 1d shows that this causes the measured OEF to be shifted to lower values. Oxygen metabolism change during hypercapnia was simulated as a 10% reduction, r$_{hc}$=0.9. Fig. 1e shows that this causes the measured OEF to shift to higher values. Changes in blood flow during hyperoxia were simulated as a 5% reduction, f_{ho}=0.95. Fig. 1f shows a minor shift to lower values of OEF under this condition.

Figure 1 - Detailed BOLD model simulation results



Discussion: Simulations predict that the measured OEF is an overestimate of the true OEF (Fig. 1a). This has been observed experimentally[7]. Comparison of the M values reveals that M$_{hc}$ overestimates M$_{ho}$ (Fig. 1c), but that a simple linear scaling can resolve this discrepancy (M$_{ho}$=0.89×M$_{hc}$). Fig. 1a also reveals that the method is relatively insensitive to variations in [Hb] (=Hct/0.03) and CBVt, as revealed by the narrow distribution of *measured* OEF values for a given actual OEF. As is the case with standard calibrated BOLD[3] accurate information regarding flow-volume coupling is critical (Fig. 1d). Changes in oxygen metabolism during hypercapnia would cause OEF to be greatly overestimated (Fig. 1e), whilst changes in blood flow during hyperoxia have a weaker effect (Fig. 1f). These effects can be minimised using tightly controlled respiratory challenges[8] to maintain low levels of hypercapnia and isocapnic hyperoxia.

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