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Sources of systematic error in calibrated BOLD based mapping of baseline oxygen extraction fraction

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ABSTRACT

Recently a new class of calibrated blood oxygen level dependent (BOLD) functional magnetic resonance imaging (MRI) methods were introduced to quantitatively measure the baseline oxygen extraction fraction (OEF). These methods rely on two respiratory challenges and a mathematical model of the resultant changes in the BOLD functional MRI signal to estimate the OEF. However, this mathematical model does not include all of the effects that contribute to the BOLD signal, it relies on several physiological assumptions and it may be affected by intersubject physiological variability. The aim of this study was to investigate these sources of systematic error and their effect on estimating the OEF. This was achieved through simulation using a detailed model of the BOLD signal. Large ranges for intersubject variability in baseline physiological parameters such as haematocrit and cerebral blood volume were considered. Despite this the uncertainty in the relationship between the measured BOLD signals and the OEF was relatively low. Investigations of the physiological assumptions that underlie the mathematical model revealed that OEF measurements are likely to be overestimated if oxygen metabolism changes during hypercapnia or cerebral blood flow changes under hyperoxia. Hypoxic hypoxia was predicted to result in an underestimation of the OEF, whilst anaemic hypoxia was found to have only a minimal effect.

Introduction

Recently a new class of calibrated blood oxygenation level dependent (BOLD) functional magnetic resonance imaging (MRI) methods were introduced to quantitatively measure the baseline oxygen extraction fraction (OEF) (Bulte et al., 2012; Gauthier et al., 2012; Wise et al., 2013). These methods rely on two respiratory challenges to induce hypercapnia and hyperoxia resulting in changes in the BOLD signal. This response is measured, alongside the accompanying changes in cerebral blood flow (CBF), using a combined arterial spin labelling (ASL) and BOLD-weighted MR imaging technique. Furthermore the change in the end-tidal partial pressure of oxygen ($P_{ET}O_2$) during hyperoxia is measured using a gas analyser. These data are combined with a mathematical model of the BOLD response (Davis et al., 1998; Hoge et al., 1999) to estimate the baseline OEF. However, we know that this model does not include all of the effects that generate the observed BOLD response and that several physiological assumptions are made in its derivation. In addition, intersubject physiological variability has the potential to cause systematic error in the estimation of the OEF. These errors are difficult to investigate experimentally as the ground truth OEF value is generally unknown. However, through detailed simulations of the BOLD signal we have shown that it is possible to get a better understanding of these sources of systematic error (Blockley et al., 2012; Griffeth and Buxton, 2011). In this study we applied this methodology to assess the robustness of OEF mapping using calibrated BOLD. Consistent with our earlier work, we considered the sensitivity of the measured signals (BOLD, CBF, and $P_{ET}O_2$), and simple combinations of these signals, to the OEF (Blockley et al., 2012). Absolute accuracy was not assessed due to the potential risk that such observations would be dependent on the precise physiological conditions used by the detailed BOLD signal model. Through these simulations we were able to demonstrate that OEF mapping using calibrated BOLD is fairly robust to large variations in baseline physiology, but that it is sensitive to changes in the cerebral metabolic rate of oxygen consumption ($CMRO_2$) and CBF during the required respiratory challenges.

Theory

In the following section the theory to convert measured changes in the BOLD signal to an estimate of the OEF is described. Initially the existing quantification method based on the Davis model is recapped. A simple model of the BOLD signal is then developed to examine the sensitivity of the hypercapnia and hyperoxia BOLD signal to specific aspects of the underlying physiology, which would otherwise be

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obscured by the non-linear form of the Davis model. Details regarding the modelling of oxygen transport and the conversion of estimates of deoxyhaemoglobin concentration to OEF are then considered.

Modelling the BOLD response using a generalised Davis model

The Davis model provides a simple description of the BOLD signal and forms the basis of the calibrated BOLD method (Davis et al., 1998). The percentage change in the BOLD signal, δs, is dependent on changes in venous CBV, v, and venous deoxyhaemoglobin concentration, $\Delta[dHb]$, where $\Delta[dHb]$ is the difference between the active and baseline deoxyhaemoglobin concentration and v is the ratio of the active and baseline venous CBV. The effect of changes in v and $\Delta[dHb]$ are scaled by the product of the echo time, TE, a constant reflecting properties of the experiment, κ, the baseline venous CBV, V_0, and the baseline venous deoxyhaemoglobin concentration, $[dHb]_0$. It is $[dHb]_0$ that determines the magnetic susceptibility of deoxygenated blood and is hence responsible for the extravascular BOLD signal that the Davis model seeks to describe.

$$\delta s = TE\kappa V_0[dHb]_0^{\beta}\left[1-v\left(1+\frac{\Delta[dHb]}{[dHb]_0}\right)^{\beta}\right] \tag{1}$$

The exponent β controls for the vessel size dependency of the transformation of changes in $[dHb]$ to BOLD signal. The value of β is magnetic field strength dependent and assumed to be 1.3 at 3 T (Mark et al., 2011). Eq. (1) can be used to describe the effect of hypercapnia and hyperoxia by modelling the changes in $[dHb]$ that occur. For hypercapnia (subscript hc) changes in $[dHb]$ are driven by an increase in CBF, where f is the ratio of the active and baseline CBF, and is accompanied by a change in v. However, changes in v are generally inferred based on a fixed coupling relationship between CBF and CBV: $v = f^{\alpha}$ (Grubb et al., 1974).

$$\delta s_{hc} = TE\kappa V_0[dHb]_0^{\beta}\left[1-f_{hc}^{\alpha-\beta}\right] \tag{2}$$

Furthermore, for hyperoxia (subscript ho) changes in $[dHb]$ are due to the increased amount of oxygen carried by arterial blood and v is assumed to be unchanged (Chiarelli et al., 2007).

$$\delta s_{ho} = TE\kappa V_0[dHb]_0^{\beta}\left[1-\left(1+\frac{\Delta[dHb]_{ho}}{[dHb]_0}\right)^{\beta}\right] \tag{3}$$

Here $\Delta[dHb]_{ho}$ is the change in $[dHb]$ due to the hyperoxic condition and can be described by modelling the transport of additional oxygen carried by the arterial blood bound to haemoglobin and dissolved within the plasma (Blockley et al., 2012).

$$\Delta[dHb]_{ho} = -\frac{\phi[Hb]\Delta SaO_2 + \varepsilon\Delta PaO_2}{\phi} \tag{4}$$

The bound component is a function of the oxygen carrying capacity of haemoglobin, $\phi = 1.34\ \mathrm{ml O_2\ g_{Hb}^{-1}}$, the haemoglobin concentration (related to haematocrit), $[Hb] \sim 15\ \mathrm{g_{Hb}\ dl^{-1}}$, and the change in arterial oxygen saturation, ΔSaO_2. This change can be calculated using the Severinghaus equation given knowledge of the arterial oxygen partial pressure, PaO_2, during normoxia and hyperoxia acquired using expired gas analysis (Severinghaus, 1979). The oxygen dissolved in plasma is dependent on the solubility coefficient of oxygen in blood, $\varepsilon = 0.003\ \mathrm{ml O_2\ dl^{-1}\ mm\ Hg^{-1}}$. By combining Eqs. (2) and (3) the baseline venous deoxyhaemoglobin, $[dHb]_0$, can be isolated using the Davis model.

$$[dHb]_0 = \frac{\Delta[dHb]_{ho}}{\left(1-\frac{\delta s_{ho}}{\delta s_{hc}}\left[f_{hc}^{\alpha-\beta}-1\right]\right)^{1/\beta}-1} \tag{5}$$

Investigating the underlying principles of the technique through a simple model

However, the standard Davis model formulation does not easily facilitate a better understanding of the underlying principles of this technique due to its non-linear nature. Therefore, we reformulate the model as described by Eqs. (2) and (3) using a linearised relationship between $[dHb]$ and the BOLD signal ($\beta = 1$) recently explored by Griffeth et al. (2013). The BOLD response to hypercapnia therefore becomes,

$$\delta s_{hc} = TE\kappa V_0[dHb]_0\left[1-f_{hc}^{\alpha-1}\right]. \tag{6}$$

With this in mind the model predicts that, for a given change in CBF and venous CBV, the hypercapnia BOLD signal is sensitive to the product of V_0 and $[dHb]_0$. Similarly the BOLD response to hyperoxia becomes,

$$\delta s_{ho} = -TE\kappa V_0\Delta[dHb]_{ho}. \tag{7}$$

As previously shown the hyperoxia BOLD signal is not dependent on the baseline $[dHb]$ level, $[dHb]_0$, (Blockley et al., 2013), hence the signal is predicted to only be sensitive to V_0. By taking the ratio of Eqs. (6) and (7), a simple relationship between experimentally measurable quantities and the baseline deoxyhaemoglobin concentration, $[dHb]_0$, is found.

$$[dHb]_0 = -\frac{\delta s_{hc}}{\delta s_{ho}}\frac{\Delta[dHb]_{ho}}{f_{hc}^{\alpha-1}-1} \tag{8}$$

This reformulation makes clear that this method for measuring $[dHb]_0$ relies on the following underlying principles: (i) the hypercapnia BOLD signal is sensitive to the product of venous CBV and the baseline deoxyhaemoglobin concentration and (ii) the hyperoxia BOLD signal is sensitive to venous CBV. By taking the ratio of these signals the baseline deoxyhaemoglobin concentration can be extracted.

The importance of accurate oxygen transport modelling

In the preceding description, changes in $[dHb]$ due to hypercapnia and hyperoxia were separately modelled as described by (Bulte et al., 2012). However, in the work of (Gauthier and Hoge, 2012) a potentially more flexible model was derived to enable the change in $[dHb]$ to be described for simultaneous changes in PaO_2 and CBF. Following this generalised calibration model (GCM) approach we can rewrite Eq. (4).

$$\Delta[dHb]_{gcm} = -\frac{\phi[Hb]\Delta SaO_2 + \varepsilon\Delta PaO_2}{\phi} + \left(\frac{1}{f}-1\right)\frac{\phi[Hb]SaO_{2,0} + \varepsilon PaO_{2,0}}{\phi}E_0 \tag{9}$$

For a hyperoxic challenge with constant CBF, Eq. (9) reduces to Eq. (4). However, for a hypercapnic increase in CBF this is not the case if the baseline oxygen saturation, $SaO_{2,0}$, is less than 1. In contrast to Eq. (4) the sensitivity of the hypercapnia method to OEF is explicitly defined by the parameter E_0. The same basic principles were also used to derive a similar model with a different mathematical form (Wise et al., 2013). However, it can be shown to be mathematically equivalent to the GCM (see Appendix A).

Fig. 1a presents $\Delta[dHb]$ as a function of the baseline partial pressure of oxygen, $PaO_{2,0}$, for a fixed 60% increase in CBF ($f = 1.6$). For typical $PaO_{2,0}$ values (100–120 mm Hg, shaded orange band in Fig. 1a) the difference between these models is less than 2%. However, with decreasing $PaO_{2,0}$ this difference increases rapidly.