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Measurement of brain oxygenation changes using dynamic T_1-weighted imaging

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ABSTRACT

Magnetic resonance imaging (MRI) has proven useful in evaluating oxygenation in several types of tissue and blood. This study evaluates brain tissue oxygenation changes between normoxia and hyperoxia in healthy subjects using dynamic T_1 and T_2^*-weighted imaging sequences. The change in F_iO_2 induced by hyperoxia caused a significant decrease in T_1. A model to determine changes in tissue oxygen tension from the T_1-weighted MRI signal is presented based on previous findings that T_1 is sensitive to oxygen tension whereas T_2^* is sensitive to blood saturation. The two sequences produce results with different regional and temporal dynamics. These differences combined with results from simulations of the T_1 signal intensities, indicate an increase in extravascular oxygen tension during hyperoxia. This study concludes that T_1 and T_2^* responses to F_iO_2 serve as independent biomarkers of oxygen physiology in the brain with a potential to provide quantitative information on tissue oxygenation.

Introduction

Maintenance of cerebral function requires an uninterrupted and consistent oxygen delivery as loss of consciousness ensues seconds after inadequate blood flow, an effect which emphasises that any reserve of O_2 is rapidly exhausted by the brain's high metabolic rate (Gjedde et al., 2005). Though it is understood that tissues and cells need to maintain oxygen concentrations to within narrow physiological ranges, these concentrations are not fully determined because the available techniques for quantitative in vivo measurements on healthy human subjects are limited.

To date, most quantitative measurements of brain tissue oxygenation ($P_{bt}O_2$) have been produced with the use of electrodes in animals or anaesthetised patients, many of which are presented in a comprehensive review of PO_2 by Ndubuizu and LaManna (2007). Three findings of interest outlined in this review are that $P_{bt}O_2$ is shown to be dependent on arterial oxygenation (P_aO_2), increases in oxygen tension during hyperoxia are greatest in sites where baseline oxygen tension is high, and that oxygen tension is very inhomogeneous on both regional and local scales. Pinpoint measurements are not only invasive, but also provide limited information of the surrounding tissue's oxygenation due to its inhomogeneous nature.

Several techniques estimating tissue oxygenation from blood oxygen saturation have been used as a non-invasive and more global alternative. Still, it is not straightforward because it depends on quantitative assumptions regarding factors such as cerebral blood volume (CBV) and cerebral blood flow (CBF), both of which vary greatly between subjects as well as between brain regions (Henriksen et al., 2012; Parkes et al., 2004; Rostrup et al., 2005). This limitation is highlighted in extensive studies which show that blood saturation is an inadequate predictor of local tissue oxygenation due to regional and microvascular variations (Griffeth and Buxton, 2011; Hlatky et al., 2008; Vazquez et al., 2010). Despite existing techniques, quantitative measurements of human $P_{bt}O_2$ are very limited and vary greatly (Ndubuizu and LaManna, 2007).

Measurement of brain oxygenation has potential widespread utility. Local ischemia has proven to be a causative factor for functional impairment in stroke and vascular dementia, and has also been implicated as a central factor for development of degenerative disease such as Alzheimer's disease. Regarding the treatment of brain tumours, studies have confirmed that the potential for diagnosis and treatment of tumours can be greatly improved using estimates of tumour oxygenation obtained from changes in oxygenation during hyperoxia (O'Connor et al., 2009a). Similarly, studies on trauma patients show that compromised oxygenation is associated with increased brain injury and that $P_{bt}O_2$ is a valuable indicator of recovery (Hlatky et al., 2008). Yet, despite the numerous clinical applications of oxygenation mapping, there is currently no adequately accurate and

Abbreviations: BOLD, blood oxygenation level dependent; CBF, cerebral blood flow; TOLD, T_1-weighted tissue oxygen level dependent; CBV, cerebral blood volume; $P_{bt}O_2$, brain tissue oxygen tension; P_aO_2, arterial oxygen tension; P_cO_2, capillary oxygen tension.

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non-invasive clinical method to measure absolute or changes in $P_{bt}O_2$ values.

Magnetic resonance imaging (MRI) has the potential to detect changes in oxygenation. There are two distinct mechanisms by which oxygen levels affect the MR signal owing that molecular oxygen and deoxy-haemoglobin are paramagnetic. T_1, T_2 and T_2^* relaxation times are influenced by paramagnetism, but the effect is highly dependent on molecular sizes and diffusivity. In general small molecules may interact sufficiently with water to affect T_1, but much less T_2 and T_2^*. Thus, the longitudinal relaxation rate R_1 ($1/T_1$) increases linearly with oxygen tension (PO_2) (Pilkinton et al., 2012; Zaharchuk et al., 2006), whilst the paramagnetic centres of deoxy-haemoglobin are so sequestered from plasma and tissue water that they have very little effect on T_1 (Brooks and Di Chiro, 1987). Deoxy-haemoglobin does, on the other hand, influence T2*, and is commonly exploited in blood oxygenation level dependent (BOLD) imaging. With respect to the T_2 value of arterial blood, it is much less affected by hyperoxia than either T_1 or T_2^* (d'Othée et al., 2003; Noseworthy et al., 1999; Tadamura et al., 1997).

Since protein concentration has little impact on the relaxivity of molecular oxygen (Pilkinton et al., 2012; Zaharchuk et al., 2005), changes in PO_2 for both intravascular and extravascular fluids produce an equivalent effect on T_1-weighted sequences (Hopkins et al., 1986). In contrast, T_2^*-weighted sequences used for BOLD imaging are sensitive to changes in deoxy-haemoglobin only and, therefore, are sensitive to changes in blood saturation alone.

The aim of this study is to detect changes in molecular oxygen concentrations in the brain during hyperoxia. We pursue this using a quantitative analysis of T_1-weighted imaging data during a hyperoxic challenge. We also obtain T_2^*-weighted imaging data in order to compare the effect of changes in blood saturation to those of changes in PO_2 levels. This is, to our knowledge, the first study of oxygenation in the human brain incorporating both T_1-weighted and T_2^*-weighted sequences. It is likely that signal changes from these two sequences will serve as complementary biomarkers of tissue microvasculature providing information about both intra- and extravascular oxygen transport. This combination can provide a powerful tool in mapping and understanding cerebral vascular oxygen supply and could lead to better diagnosis and treatment of brain disorders involving reductions in brain oxygenation.

Theory

In the following we will estimate the change in MR signal from a T_1-weighted imaging sequence induced by hyperoxia. We consider the longitudinal relaxation rate R_1 as a function of PO_2:

$$R_1(PO_2) = R_1(0) + r_{1,ox}\cdot PO_2 + r_{1,dHb}\cdot[dHb] \tag{1}$$

where PO_2 is the partial pressure of molecular oxygen and [dHb] is the concentration of deoxy-haemoglobin. $R_1(0)$ is the longitudinal relaxation rate in the absence of effects due to molecular O_2 or deoxy-haemoglobin, $r_{1,ox}$ is the longitudinal relaxivity of molecular oxygen and $r_{1,dHb}$ is the relaxivity of deoxy-haemoglobin. Previous studies have determined the relaxivity of dissolved oxygen in fluids and found a value of $r_{1,ox} = 1.21 \times 10^{-3}\ s^{-1}kPa^{-1}$ for both blood and CSF (Pilkinton et al., 2012) whilst the effect on R_2 was found to be negligible (Pilkinton et al., 2011). The relaxivity for deoxy-haemoglobin has been measured in a similar fashion to be $r_{1,dHb} = 1.46 \times 10^{-2}\ s^{-1}\ mM^{-1}$(Blockley et al., 2008) which amounts to a small effect on R_1, but is still included in this study for improved accuracy.

The T_1-weighted imaging data in the present study are obtained from a saturation recovery (SR) sequence with centric phase encoding (Larsson et al., 2008). The MR signal can be described by the signal equation:

$$S(PO_2) = M_0\left(1-e^{-T_d\cdot R_1(PO_2)}\right). \tag{2}$$

Here, S is the amplitude of the MR signal, M_0 is the longitudinal magnetisation and T_d is the saturation delay time. This equation demonstrates that the percent change in signal is dependent on the intrinsic R_1 of the tissue during breathing of room air and the change in R_1 after raising the oxygen concentration.

For the present purpose, we shall consider the voxel as composed of three vascular compartments (arterial, capillary and venous) and one tissue compartment. The magnitude of the resulting signal change will depend on the PO_2 change in each of these compartments, as well as the efficiency of water exchange between them. Changes in CBV due to hyperoxia are considered negligible as it has been shown to vary little during hyperoxic challenge (Kolbitsch et al., 2002; Lu et al., 2009).

During inhalation of hyperoxic gas the PO_2 will increase considerably on the arterial side of the vascular tree, but the change in venous oxygen PO_2 is two orders of magnitude smaller due to haemoglobin binding.

In the present study we will assume the capillary compartment PO_2 is intermediary to the arterial and venous compartments, and we will consider conditions of both fast and slow water exchange, as well as conditions under which $P_{bt}O_2$ is unaffected by hyperoxia, or changes proportionally with capillary oxygen tension (P_cO_2).

Under the assumption of no water exchange the combined signal from a voxel can be expressed as a sum of the signals from each compartment:

$$\Delta S_{voxel} = \sum_{i=a,c,v,t} v_i\cdot\Delta S_i \tag{3}$$

where the subscripts a, c, v, and t refer to the arterial, capillary and venous tissue compartments, and v_i is the fractional volume of compartment i.

In the limit of fast water exchange, the resulting change in R_1 can be expressed as:

$$\Delta R_1 = \sum_{i=a,c,v,t} v_i\cdot\Delta R_{1,i}. \tag{4}$$

The effect of water exchange is dependent on the MR imaging strategy, concentration differences and timing. With the use a of saturation recovery sequence in the present study, the effect varies with the saturation delay (T_d) (Larsson et al., 2001). In the limit where T_d is much smaller than the water exchange time, the amount of water exchange tends towards zero and the overall MR signal can be evaluated by Eq. (3). When the delay time is long enough to permit a fast exchange system, however, a voxel can be considered as one compartment with a single R_1 value equal to the weighted sum of R_1 from each contributing compartment (Donahue et al., 1997).

Using literature values for R_1 in different tissue types and blood volume distributions it is possible to estimate the expected magnitude of signal change under the different scenarios described above (Eq. (2)). We used an approximated R_1 value of $0.57\ s^{-1}$ for blood under normoxic conditions, as well as values of $1.16\ s^{-1}$ and $0.67\ s^{-1}$ for white and grey matter. Furthermore we used the relaxivity values mentioned above and assumed a change in P_aO_2 from approximately 16 to 70 kPa with the associated changes in deoxy-haemoglobin concentration during inhalation of 100% O_2 (Rostrup et al., 1995). The oxygen dissociation curve was calculated according to Winslow et al. (1983). Relative fractional volumes of 25%, 25% and 50% have been assumed for the arterial, capillary and venous compartments (Piechnik et al., 2008). T_d in Eq. (2) is set to the experimentally used value of 0.612 s.