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Noninvasive quantification of cerebral blood volume in humans during functional activation

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Like cerebral blood flow (CBF), cerebral blood volume (CBV) is an important physiological parameter closely associated with brain activity and thus, noninvasive quantification of CBV during brain activation provides another opportunity to investigate the relationship between neuronal activity and hemodynamic changes. In this paper, a new method is presented that is able to quantify CBV at rest and during activation. Specifically, using an inversion recovery pulse sequence, a set of brain images was collected at various inversion times (TIs). At each TI, functional images were acquired with a block-design visual stimulation paradigm. A biophysical model comprised of multiple tissue components was developed and was utilized for the determination of CBV using the visual stimulation data. MRI experiments on five healthy volunteers showed that CBV was 5.0 ± 1.5 ml blood/100 ml brain during rest and increased to 6.6 ± 1.8 ml blood/100 ml brain following visual stimulation. Furthermore, experiments with visual stimulation at two frequencies (2 and 8 Hz) showed that the increases in CBV correlated with the strength of stimulation. This technique, with its ability to measure quantitative CBV values noninvasively, provides a valuable tool for quantifying hemodynamic signals associated with brain activation.
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Introduction

Functional magnetic resonance imaging (fMRI) techniques based on local cerebral hemodynamic changes have been used extensively for mapping functional neuroanatomy (Ogawa et al., 1990; Belliveau et al., 1991; Detre et al., 1992). Although there are emerging methods to measure changes in the MRI signal directly caused by neuronal action potentials (Bodurka and Bandettini, 2002; Xiong et al., 2003), the vast majority of fMRI experiments measure changes in cerebral blood oxygenation (Ogawa et al., 1992; Kwong et al., 1992; Bandettini et al., 1992; Frahm et al., 1992), blood flow (Williams et al., 1992; Edelman et al., 1994; Kim, 1995; Kwong et al., 1995), or blood volume (Belliveau et al., 1991; Mandeville et al., 1998) as an indirect measure of neuronal activity. Hemodynamic-based fMRI signals have different characteristics in terms of sensitivity and specificity in detecting brain activity. Techniques based on BOLD (blood oxygenation level-dependent) contrast usually have higher sensitivity; however, physiological interpretation of the BOLD signal is limited since the signal arises from the complex interplay of blood volume, flow and oxygen consumption (Ogawa et al., 1993; Boxerman et al., 1995; Buxton et al., 1998; van Zijl et al., 1998). Perfusion imaging with arterial spin labeling (ASL) provides quantitative measurement of cerebral blood flow (CBF) that targets signal changes more closely associated with neuronal activity compared to the relatively venous-weighted blood oxygenation. However, sensitivity of current ASL perfusion techniques is inherently low due to the low perfusion-related contrast (~1%) and the image subtraction procedure (Wong et al., 1997). The earliest human fMRI experiment was performed with injections of exogenous susceptibility contrast agents (Belliveau et al., 1991). Although this method has not been widely used in human studies, primarily due to the invasiveness of the technique and the short half-lifetime of Gadolinium (Gd)-based contrast agents, it has been successfully employed in animal fMRI experiments utilizing the much longer half-lifetime monocrystalline iron oxide nanocolloid (MION) (Mandeville et al., 1998). Recently, a noninvasive fMRI technique based on CBV changes during brain activation was proposed (Lu et al., 2003), in which MR signals of blood water were suppressed by acquiring images at the blood-nulling point of an inversion recovery sequence to detect vascular space occupancy (VASO)-dependent signal changes associated with brain activation. VASO imaging is expected to have better spatial specificity than BOLD due to its high sensitivity to microvessels, but it cannot obtain

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quantitative CBV information during activation without additional baseline CBV data.

Noninvasive quantification of CBV and its change during physiological challenges promise to improve our understanding of brain hemodynamics and fMRI signal mechanisms, including evaluating potential alterations of vascular state versus neuronal activation following drug administration (Salmeron and Stein, 2002). However, CBV imaging with injections of exogenous contrast agents is an invasive method and is not suitable for fMRI studies with complex stimulation paradigms (Belliveau et al., 1991), while VASO imaging detects CBV-weighted signal changes between rest and activation states, but does not provide absolute CBV values at these two states (Lu et al., 2003).

We present here a new method that is able to quantify CBV noninvasively at rest and during activation. This was achieved by measuring fMRI signal at various inversion times (TI), thereby varying the weightings of CBV and blood oxygenation contrasts. The data were fitted to a biophysical model comprised of multiple tissue components to obtain absolute CBV at rest and following activation. Functional experiments with graded visual stimulation were conducted on healthy volunteers to evaluate this method.

Methods

Biophysical model for determination of CBV and blood oxygenation

A three-compartment model was used, in which a voxel in the activated region contains F_{CSF} fraction of cerebral-spinal fluid (CSF) and 1-F_{CSF} fraction of brain parenchyma. The parenchyma, in turn, contains f_b fraction (also known as CBV) of blood and 1-f_b fraction of extravascular tissue. Note that the volume fraction of the blood in the whole voxel is given by:

$$F_b = (1 - F_{CSF}) \cdot f_b \tag{1}$$

The MR signal magnitude can be written as:

$$S = \mathrm{abs}(S_{CSF} + S_b + S_t) \tag{2}$$

where S_i (i = CSF, b or t) is the signal contribution from the compartment of CSF, blood and tissue, respectively, and abs denotes the absolute value. Considering the volume fractions, water proton densities and MR relaxation rates, the signals from individual compartments are given by:

$$S_{CSF} = F_{CSF} \cdot C_{CSF} \cdot M_{CSF}(\mathrm{TI}) \cdot e^{-\mathrm{TE} \cdot R^*_{2,CSF}} \tag{3}$$

$$S_b = (1 - F_{CSF}) \cdot f_b \cdot C_b \cdot M_b(\mathrm{TI}) \cdot e^{-\mathrm{TE} \cdot R^*_{2,b}} \tag{4}$$

$$S_t = (1 - F_{CSF}) \cdot \left(C_p - f_b \cdot C_b\right) \cdot M_t(\mathrm{TI}) \cdot e^{E(\mathrm{TE})} \tag{5}$$

where C_i (i = CSF, b or p) is the water proton density for CSF, blood and parenchyma, respectively. Note that Eq. (5) is slightly different from Eq. (4) in the water content calculation because the water density values in the literature usually refer to parenchyma, not pure extravascular tissue. M_i(TI) is the signal dependence on longitudinal relaxation rate (R_1) during an inversion recovery experiment:

$$M(\mathrm{TI}) = 1 - 2 \cdot e^{-\mathrm{TI} \cdot R_1} + e^{-\mathrm{TR} \cdot R_1} \tag{6}$$

where TI is the inversion time and TR is the repetition time.

Notice that the exponent of the transverse relaxation term in Eq. (5) is not a conventional linear function of TE because it has been shown that, in the extravascular tissue compartment, part of the transverse relaxation is quadratically dependent on TE at short echo times (Yablonskiy and Haacke, 1994; Lu and van Zijl, 2005). More specifically,

$$E(\mathrm{TE}) = -f_b \cdot V(\delta\omega \cdot \mathrm{TE}) - R^*_{2,\mathrm{other}} \cdot \mathrm{TE} \tag{7}$$

where the first term in Eq. (7) denotes the signal decay due to blood, and $R^*_{2,\mathrm{other}}$ includes other relaxation processes, such as pure R_2 and field inhomogeneity. $\delta\omega$ is the frequency shift due to deoxyhemoglobin and can be written as:

$$\delta\omega = \gamma \cdot B_0 \cdot \frac{4}{3}\pi \cdot \Delta\chi \cdot \mathrm{Hct} \cdot (1 - Y_b) \tag{8}$$

where γ is the gyromagnetic ratio, B_0 is the field strength, $\Delta\chi$ is the susceptibility difference between fully oxygenated and deoxygenated blood (0.2 ppm), Hct = 0.42 × 85% = 0.357 is the estimated hematocrit in the microvasculature, and Y_b is the averaged blood oxygenation.

Note that the averaged blood oxygenation in the activated voxels is dependent on the fMRI techniques used and the activation detection criteria. For example, when ASL fMRI is used, the activated voxels are expected to contain more arterial blood. When VASO (at blood-nulling TI) is used, the blood content is likely to consist of a combination of arterial and venous blood similar to that in microvasculature, i.e., 30% arterial and 70% venous blood. When BOLD fMRI is used, it is expected to contain mostly venous blood (Lai et al., 1993), especially when using a gradient-echo sequence. For the data acquired in this study, considering that the activation map is a combined contrast between BOLD and CBV with only one out of fourteen experiments acquired at the blood-nulling TI, it is believed that the voxel detection is mainly due to the venous BOLD contrast. However, it is important to point out that the venous contrast mechanism used in the detection does not necessarily suggest that the BOLD-activated voxels contain only venous vessels. Given the relatively large voxel size used in the fMRI experiments with additional spatial smoothing, it is highly likely that certain number of arterial vessels are present in the voxel, even though they do not contribute to the BOLD signal changes. The precise amount of partial voluming between arterial and venous blood is hard to determine and may be variable from subject to subject, we therefore evaluated the fitting parameters using a range of assumed Y_b values and studied the dependence of CBV results on this assumption.

The function $V(x)$ in Eq. (7) is an integration (Eq. A16 in Yablonskiy and Haacke, 1994) and can be approximated by:

$$V(x) = 0.3 \cdot x^2 \quad \text{when } x < 1.5 \tag{9a}$$

$$V(x) = x - 1 \quad \text{when } x \geq 1.5 \tag{9b}$$

Note that the transition TE value (see Eq. (7)), $1.5/\delta\omega$, is dependent upon Y_b. For physiologically relevant Y_b range (0.61 to 0.98), this corresponds to TE = 16 ms at Y_b = 0.61 and TE = 312 ms at Y_b = 0.98. Therefore, for the experimental data (TE = 7.6 ms) obtained in the present study, Eq. (9a) should be used in calculation.