Towards the Measurement of Relative CBV Using BOLD Contrast and Mild Hypoxia

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Introduction

A common method for measuring relative cerebral blood volume is to inject a bolus of paramagnetic contrast agent (typically Gd-DTPA). We have investigated a potential alternative method using a mild hypoxic challenge in conjunction with a gradient-echo BOLD imaging approach. Van Zijl *et al* [1] have previously reported a method using spin-echo signal changes in the cat brain induced by hypoxia.

Mild hypoxia will result in a small decrease in oxygen saturation without significant increases in cerebral blood flow (CBF) [2]. Since we expect no change in cerebral blood flow (CBF) or oxygen consumption ($CMRO_2$) between normoxia and mild hypoxia, we predict that the change in arterial oxygen saturation would result in a proportional change in venous oxygenation with no change in CBV. According to Ogawa *et al* [3], the contribution to the BOLD effect in the extravascular water compartment in a gradient echo experiment may be described by $R2^*_{BOLD}=k\{Hct(1-Y)\}^{\beta}CBV$ where k is a field dependent constant, Hct is the haematocrit, Y is the fractional blood oxygenation, β is of order 1-2 and CBV is the blood volume fraction of capillary and venous vessels. In a gradient-echo experiment, the measured signal is proportional to exp(-TE R2*) where TE is echo time. Therefore, under small changes in R2* (ΔR2*) resulting from hypoxia, the fractional signal change may be modeled as $\Delta S/S_0 \approx -\Delta R2^* TE$. This implies that $\Delta S/S_0$ is directly proportional to CBV. We use this relationship when comparing BOLD signal changes induced by mild hypoxia to estimate relative CBV ratios between cerebral cortical grey matter, white matter and deep grey matter.

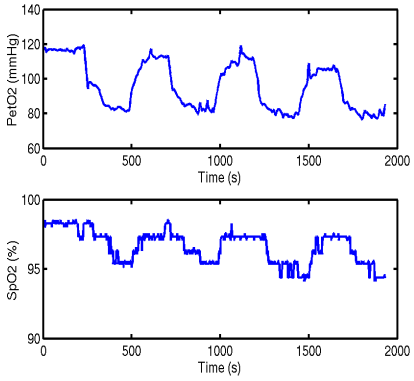
Methods

Eight volunteers (2 female) aged 31 ± 6 years (mean±SD) underwent gradient-echo echo-planar imaging at 3T (Varian Unity Inova) using a hybrid interleaved BOLD contrast / pulsed arterial spin labeling (PASL) imaging sequence. 1108 volumes were acquired (TR=1.75s, in-plane resolution 4x4 mm, five 6 mm thick axial slices extending in a superior direction from the thalamus). TE=32ms for BOLD acquisition. A QUIPSS2 [4] sequence was used for relative measurements of CBF to identify potential changes under mild hypoxia (TE=22ms, tag-excitation time (TI2) 1.4s, tag-saturation time (TI1) 0.7s, 10cm inversion slab 1.5cm from the imaging slab). A T1 weighted whole-brain structural scan was also acquired. Subjects breathed an inspired oxygen fraction of 21% (normoxia) or 16% (mild hypoxia), switched every 4 minutes. End-tidal oxygen ($P_{ET}O_2$) and carbon dioxide ($P_{ET}CO_2$) were recorded (AEI Technologies, PA) as a measure of arterial tensions of oxygen and carbon dioxide. Arterial oxygen saturation (SpO_2) was recorded using digital pulse oximetry (MR Equipment Corp. Multigas 9500).

The MR data were motion corrected (FEAT, FMRI Expert Analysis Tool [5]). BOLD data were high-pass temporally filtered. Fractional signal changes with hypoxia were expressed relative to the mean of the first 60 volumes acquired during normoxia. Mean time-courses from cortical grey matter, deep grey matter and white matter regions were extracted. After registration to T1 weighted structural scans, segmentation of the EPI images by tissue class was performed using FAST (FMRIB automated segmentation tool [6]) with thresholded normoxic CBF data incorporated into the segmentation to further discriminate grey matter (high CBF) from white matter (low CBF). The BOLD signal time-courses were regressed (FMRIB improved linear model [7]) against the recorded $P_{ET}O_2$ and $P_{ET}CO_2$, to measure the change in BOLD signal for a unit change in partial pressure of oxygen. $P_{ET}CO_2$ was included as a potential factor that may alter CBF [8]. Incorporated into this regression was an empirically determined 30.5s delay for changes in BOLD signal following a measured change in $P_{ET}O_2$. This was established from the maximum of the group mean cross-correlation performed between BOLD signal and $P_{ET}O_2$. A 6s delay of the BOLD signal was incorporated for the $P_{ET}CO_2$ regression, established in a previous study [8]. It should be noted that the CBV relationship above depends on fractional oxygenation (Y). Despite this, we chose to compare MR signal changes to $P_{ET}O_2$ changes rather than SpO_2. This is because of the comparatively poor digital resolution of recorded SpO_2 (figure), its blurring and temporal delay caused in part by temporal averaging in our monitor. Although the oxygen dissociation relationship is nonlinear over large ranges, over the small range of oxygen saturation changes observed here, an assumption of linearity between $P_{ET}O_2$ and arterial oxygen saturation appears reasonable (figure).

CBF-sensitive (PASL) image volumes were pair-wise subtracted to yield time-series with image intensity assumed proportional to local CBF. As for the BOLD data, CBF signal was averaged over regions of interest and normalized to the initial normoxic period. Frontal and occipital areas were manually excluded from CBF calculations because of image ghosting. Regression was performed as for the regional BOLD signals to identify potential hypoxia-induced regional changes in CBF.

Results and Discussion



Physiological recordings from one volunteer. The upper graph shows end-tidal oxygen $P_{ET}O_2$ and the lower graph shows oxygen saturation (SpO_2).

Group mean SpO_2 fell from 97.5±0.9% during normoxia to 94.5±1.3% during the hypoxic periods (mean±SD across subjects) with corresponding $P_{ET}O_2$ values of 111.0±3.5 mmHg and 82.6±4.3 mmHg respectively. This represents a significant (P<0.01) but mild hypoxic challenge. There was a statistically significant regression (one-tailed P<0.05) between regional BOLD signal and $P_{ET}O_2$ in 7 out of the 8 subjects imaged, for all three regions. The BOLD signal was observed to decrease during hypoxic periods as expected from the equations quoted above.

	$\Delta S_{BOLD}/\Delta P_{ET}O_2$ (%/mmHg)	Equivalent $\Delta S_{BOLD}/\Delta SpO_2$ (%/%)
Cortical grey matter	$[1.5\pm0.7]\times10^{-2}$	$[1.5\pm0.9]\times10^{-1}$
Deep grey matter	$[9.9\pm3.8]\times10^{-3}$	$[9.8\pm4.4]\times10^{-2}$
White matter	$[1.4\pm0.4]\times10^{-2}$	$[1.3\pm0.5]\times10^{-1}$

Fractional change in BOLD signal with changes in oxygenation for different brain regions (mean±SD).

The group mean (±SD across subjects) ratio for the BOLD signal change in cortical grey matter compared to white matter was 1.57±0.56. For cortical grey compared to deep grey matter the ratio was 1.13±0.53. If these ratios are taken to represent relative CBV, they are in broad agreement with values reported in the literature in previous MRI studies using alternative methods: grey/white matter CBV ratio has been reported in the range 1.4-2.4 and cortical/deep grey ratio as 1.1 [9].

In 7 out of 8 subjects no statistically significant changes in CBF were detected. We estimated an 80% power to detect a 16% increase in grey matter CBF induced by hypoxia, at a significance level of P<0.05. It is likely therefore that CBF did not change with hypoxia. This is in agreement with literature reports suggesting that an increase in middle cerebral artery blood velocity is only observed when SpO_2 falls below 90% [2].

The proportionality between fractional BOLD signal change and CBV relies on the hypoxic challenge being mild enough not to change either CBF or $CMRO_2$. Such a challenge may be conveniently and safely delivered. The hypoxia will induce a change in BOLD signal from arterial vessels as well as venous vessels as the concentration of de-oxyHb rises on the arterial side. The measured CBV has a mixed arterial and venous contribution which could be modeled to improve quantitation. Intravascular contributions also could be estimated explicitly when calculating CBV from BOLD signal change with hypoxia. The method appears to be a promising way of mapping of relative CBV that could find clinical applications.

References

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