Measurement of Cerebral Blood Volume Using Hyperoxic Contrast

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Introduction

The gold standard method for measuring cerebral blood volume (CBV) with MRI is dynamic susceptibility contrast MRI, which relies on injecting a bolus of paramagnetic contrast agent into the blood stream, and tracking the induced signal changes (2). As well as requiring an intravenous injection, the DSC MRI method also relies on calculating an arterial input function for the subject, which can be quite challenging. Other non-invasive methods using inversion recovery and modelling have been proposed to measure CBV changes during functional activation (3) but these are relatively time consuming, requiring multiple inversion times, and have not yet been integrated into simultaneous acquisition sequences (such as BOLD/CBF).

In this study we hypothesized that CBV could be measured via the BOLD signal changes that are induced when the subject breathes an altered concentration of oxygen in their inspired gas mixture. Breathing hyperoxic gas mixtures has proven to be a safe and effective method of obtaining image contrast in T_2^* weighted MRI scans (4-6). In this paper we show that by combining a paradigm of 50% inspired oxygen with normoxic blocks during a BOLD/ASL dual acquisition sequence, it is possible to obtain BOLD, perfusion and CBV data within a single session with an effectively non-invasive procedure. CBV may be calculated using a method originally developed for a slow infusion of an intravascular contrast agent (7) which compares the signal strength during the baseline period with the steady-state signal reached during infusion, normalized to a primarily blood-filled voxel. Due to the relatively fast washout time achieved with the hyperoxic contrast used in the present study a more robust boxcar design can be employed instead of a single infusion, leading to a more efficient estimation.

Methods

In a pilot study images were acquired from 6 subjects (4 male, mean age 29±3.7 yrs) using a combined Pulsed ASL (Q2TIPS) and gradient echo EPI BOLD sequence on a 3T Siemens Trio, with an 8-channel head coil. The paradigm consisted of 2 x 6-minute blocks of hyperoxia, separated by 6 minutes of normoxia in a 28 minute protocol. Pre-processing was performed using FSL (8). The BOLD data were then masked using segmented grey and white matter masks from high-resolution structural images and analysed in Matlab. The CBV was calculated using an adaptation of the equation presented by Newman et al (7), where ρ (the density of brain tissue) is 1.04 g/ml; $h = (1 - Hct)/(1 - r * Hct)$ corrects for the fact that the haematocrit is greater in large vessels than in brain microvasculature (9), r was assigned a value of 0.85 based on PET data, n is the number of ratios measured within that portion of the infusion during which the ratio is stable, $S_r(j)$ and $S_v(j)$ are the jth signal measurements during the plateau portion in the tissue voxels and vein voxels, respectively, and $S_{r,0}$ and $S_{v,0}$ are the average signals in tissue and vein during the baseline period prior to arrival of the hyperoxic contrast. Unlike the contrast achieved with a gadolinium infusion contrast, the strongest contrast with hyperoxia occurs in veins with less contrast in arteries. This is due to the contrast arising from changes in deoxyHb:oxyHb, and SaO_2 is already at approximately 98% in arteries during normoxia. Axial slices were chosen as the sagittal sinus vein is very easy to locate and often completely encompasses more than one voxel and is thus ideal for calculating the denominator of the equation.

$$CBV = \frac{h}{n\rho}\sum_{j=1}^{n}\left(\frac{-\ln\left(\frac{S_r(j)}{S_{r,0}}\right)}{-\ln\left(\frac{S_v(j)}{S_{v,0}}\right)}\right)$$

Results and Discussion

Figure 1b shows the CBV map of a single axial slice from a representative subject. When compared with the high-resolution structural image (Figure 1a) it is clear that grey matter areas have a significantly higher CBV than white matter regions, as expected. The mean CBV was calculated to be 3.77±1.05 ml/100g globally, 3.93±0.90 ml/100g in grey matter, and 2.52±0.78 ml/100g in white matter. The mean GM/WM ratio was thus found to be 1.56. These values are found to be in close agreement with previous studies (see Table 1, other data from Roland 1993, page 483 (1)). The experimental paradigm was designed to produce no net change in CBF with increased levels of inspired oxygen. Accordingly, no significant change in the mean ASL signal due to increased FiO_2 was detected.

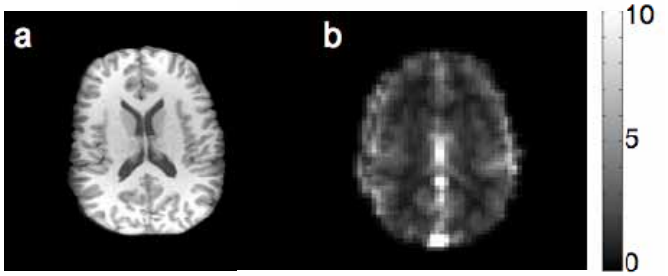

Figure 1: (a) MPRAGE structural image and (b) hyperoxia CBV map of the same slice (from coregistered images) from a typical subject. Scale is in ml blood /100g tissue.

		CBV ml/100g		
Study	n	Global	Grey Matter	White Matter
Hyperoxia	6	3.77±1.05	3.94±0.90	2.52±0.78
Grubb et al	8	4.3	-	-
Phelps et al	5	4.2±4.0	-	-
Lammertsma et al	8	-	5.9±6.6	2.4±0.3
Yamaguchi et al	14	-	4.3±0.5	2.2±0.6
Perlmutter et al	32	4.5±0.1	-	-
Roland et al	11	4.7±0.5	4.9±0.5	2.4±0.6

Table 1: Comparison of values measured using hyperoxic technique and other standard methods (1)

The global CBV value and that for grey matter are lower than expected but still within the experimental error of the other studies quoted. This may in part be due to the greater sensitivity to capillary and venous compartments, and lack of sensitivity to the arteriole and arterial contribution. This lower value contributes to the GM/WM ratio also being smaller than expected. However; the values are comparable to those obtained in a SPECT study which also compared the CBV during normoxia and during inhalation of 50% oxygen, which found that the global CBV during normocapnia and inhalation of 50% O_2 was 4.17±0.56 ml/100g (10).

Conclusions

We have demonstrated the efficacy of inspired oxygen as a non-invasive intravascular contrast agent in combination with a model of steady-state contrast. The technique has been shown to be in very good agreement with other recognised methods of measuring cerebral blood volume. The hyperoxia contrast method has several significant advantages over conventional CBV techniques: it can be repeated immediately; the absence of need of an intravenous bolus injection of paramagnetic contrast agent, making it suitable for patients for whom these are contraindicated; and that it can be used in conjunction with studies already employing respiratory-based stimulation or contrast such as those attempting metabolic measurements.

References

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