A new method for measuring changes in venous cerebral blood volume using hyperoxia

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INTRODUCTION – Venous cerebral blood volume (CBVv) is key to the BOLD response, but could not be measured directly until the advent of VERVE (1). Here we present a new method for measuring changes in CBVv on activation using hyperoxia. Hyperoxia occurs when the fraction of inspired oxygen (F_IO_2) is greater than 0.21. As the arterial blood is almost fully saturated the additional oxygen is carried in the plasma and results in an increase in venous blood saturation.

THEORY – Previous studies have measured the change in total CBV in response to a stimulus using an infusion of contrast agent and T_2^* mapping (2). Here we use hyperoxia in place of a contrast agent to limit sensitivity to the venous volume (3). We assume that increasing F_IO_2 above normal levels does not cause a significant change in arterial blood oxygen saturation, but leads to an increase in venous oxygen saturation, ΔS_v, and hence intravascular susceptibility. We also assume that ΔS_v is independent of initial oxygen saturation, i.e. we are in the linear range of the dissociation curve (4). Assuming that the associated signal change is extravascular in origin the change in R_2^* (ΔR_2^*) due to hyperoxia can be modelled for resting (Eq. 1) and activated states (Eq. 2), where κ is a constant reflecting geometry and magnetic field, χ_d is the volume susceptibility of deoxygenated blood, V_v is resting CBVv and ΔV_v is the change in CBVv on activation. The relative change in CBVv time course ($r\Delta CBVv$) is given by Eq. 3 and the fractional change in CBVv ($\Delta CBVv$) is given by Eq. 4. However an increase in the concentration of paramagnetic oxygen in the respiratory system resulting from the increase in F_IO_2 could cause additional macroscopic field inhomogeneities, leading to an additional change in R_2^* on hyperoxia ΔR_2^{*m} (5). Assuming this macroscopic contribution to R_2^* is an additive term, then the change in R_2^* on hyperoxia can be re-written as Eq. 5. The macroscopic terms cancel for Eq. 3 as they are equal for the rest and active conditions, but do not cancel in the denominator of Eq. 4 leading to a potential error in the calculation of $\Delta CBVv$.

$$\Delta R_2^{*rest} = R_{2norm}^{*rest} - R_{2hyper}^{*rest} = \kappa \Delta S_v \chi_d V_v \quad [1]$$

$$\Delta R_2^{*act} = R_{2norm}^{*act} - R_{2hyper}^{*act} = \kappa \Delta S_v \chi_d (V_v + \Delta V_v) \quad [2]$$

$$r\Delta CBVv = \Delta R_2^{*act} - \Delta R_2^{*rest} = \kappa \Delta S_v \chi_d \Delta V_v \quad [3]$$

$$\Delta CBVv = \frac{\Delta R_2^{*act} - \Delta R_2^{*rest}}{\Delta R_2^{*rest}} = \frac{\Delta V_v}{V_v} \quad [4]$$

$$\Delta R_2^* = \left(R_{2norm}^*\right) - \left(R_{2hyper}^* + \Delta R_{2hyper}^{*m}\right) \quad [5]$$

METHOD – Seven healthy subjects were scanned using a Philips Achieva 7.0 T equipped with a volume transmit and 16-ch SENSE coil. Ten dual echo GE-EPI slices covering the motor cortex were acquired, 2x2x3mm^3 resolution, SENSE 2, TE=16/46ms, TR=2.4s. Stimulus consisted of 10 cycles of finger tapping (12s ON, 19.2s OFF) at each F_IO_2. Two F_IO_2 levels of 0.21 (*norm*) and 0.60 (*hyper*) supplied using a SGD mask, allowing end-tidal CO_2 level to be maintained constant at each F_IO_2 level (6). rΔCBVv was calculated on a voxel-by-voxel basis using Eq. 3. BOLD activation maps were created from the 2nd echo data using FEAT and clusters of activation were formed (clustered $p<0.05$). Initial analysis demonstrated both positive and negative changes in $r\Delta CBVv$ in the BOLD cluster. Therefore the cluster was subdivided into regions with positive or negative $r\Delta CBVv$. These regions were used to create an average time-courses across all subjects.

RESULTS – Fig. 1a shows the $r\Delta CBVv$ time-course averaged over all subjects. Fig. 1b shows the percent change in BOLD T_2^* for the same voxels. Error bars display the intersubject standard error.

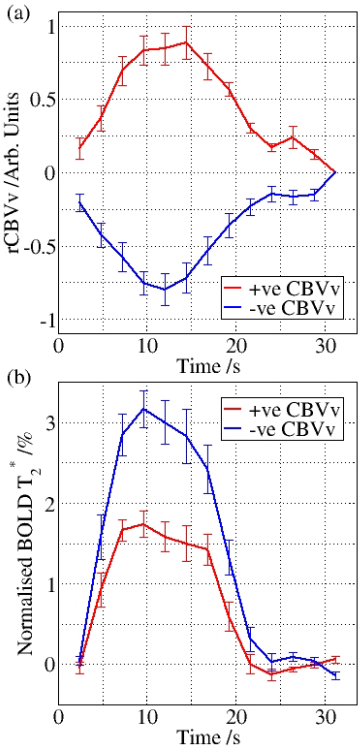

Fig.1 –Time-course averaged across subjects for BOLD activated voxels showing positive/negative CBVv changes displaying (a) rCBVv and (b) normalised BOLD T_2^* at normoxia.

DISCUSSION – We have measured changes in $r\Delta CBVv$ using hyperoxic contrast. We have not presented percentage $\Delta CBVv$ time-courses since we do not have sufficient multiecho data at rest and hyperoxia to correct the data for the effects of macroscopic field inhomogeneities (7). Negative changes in $r\Delta CBVv$ on activation were observed. The BOLD response of the voxels with negative $r\Delta CBVv$ was significantly larger ($p<0.001$) than for voxels with positive $r\Delta CBVv$. We are working to confirm the source of these apparent negative. Artifactual negative changes could be produced if ΔS_v is different for the active and passive conditions, despite simulations that predict it to be constant. This would be expected to occur most in voxels with a large BOLD signal change. This will be tested in future using graded hyperoxia and graded stimuli. Physiological negative changes could be caused by changes in the balance of intra- and extravascular pressure on the elastic venous vessel walls. It is well known that arterial blood volume (*CBVa*) increases on activation (8), which could cause an increase in extravacular pressure leading to reduced *CBVv*. The resulting BOLD signal might be expected to be largest for voxels with negative $r\Delta CBVv$, as this would reduce the deoxyhaemoglobin concentration of the blood (9). This will be tested in future by spatial comparison of maps of *CBVa* change on activation with maps of *CBVv* change.

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