A new approach for venous blood oxygenation and calibrated BOLD using hyperoxia

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Introduction: Calibration of the BOLD signal is an important goal in neuroimaging. A number of methods have been proposed to achieve this using hypercapnic (1) or hyperoxic (2) challenges. However these methods all use an assumed value of Grubbs constant (α) (3) to estimate the change in venous cerebral blood volume (*vCBV*). Here we propose a new calibration method based on hyperoxia that directly estimates the venous blood volume, oxygenation and $CMRO_2$ changes on activation. For hyperoxia, where inspired oxygen fraction > ~21%, increasing arterial oxygen partial pressure (PaO_2) increases venous oxygen saturation (Y_v) and the gradient-echo MR signal (4). This hyperoxic contrast has previously been used for BOLD calibration (2) and the measurement of *vCBV* (5,6). We show that if a functional task is performed at both normoxia and hyperoxia, the relative change in Y_v due to a task can be measured; if the task-related CBF change is also measured then $CMRO_2$ can be estimated.

Theory: Assuming a unity power law relationship between blood susceptibility and R_2* (β), valid at high field (7,8), the tissue transverse relaxation rate at rest (R_2*_{rest}) and on activation (R_2*_{act}) is given by:

$$R_2*_{rest} = kVQ\cdot(1-q_h)+R_0$$

$$R_2*_{act} = k\cdot(V+V_{act})\cdot Q\cdot(1-q_h-q_{act})+R_0$$

where k is a constant depending on field strength, vessel geometry and the susceptibility of deoxyhaemoglobin, R_0 the transverse relaxation rate of tissue containing fully oxygenated blood, V the *vCBV* at rest and V_{act} the absolute change in *vCBV* on activation, Q (= 1- Y_v) is the concentration of deoxyhaemoglobin at rest, q_{act} and q_h are the relative changes in [*dHb*] due to activation and hyperoxia respectively. The gradient of R_2*_{rest} versus (1-q_h) (rest calibration curve) is kVQ which is the '*M* factor' described for hyperoxia (2) and hypercapnia (1). The gradient of R_2*_{act} against (1-q_h) (activation calibration curve) is $k(V+V_{act})Q$, which we shall call *M′*. If the absolute value of $Q(1-q_h)$ during hyperoxia is estimated from measured end tidal lung oxygenation ($P_{ET}O_2$) (2), then the difference in the intercept of the rest and activation calibration curves is $k(V+V_{act})Qq_{act}$, which can be divided by *M′* to give q_{act}. The ratio of *M′*/*M* also gives ($1+V_{act}/V$), the change in *vCBV* on activation (6).

Methods: The local ethics committee approved the study and all subjects gave consent. 3 male and 4 female volunteers aged 26±3 yrs were scanned on a Philips Achieva 7T system (volume transmit and 16 channel receive coil). End-tidal O_2 ($P_{ET}O_2$) and CO_2 ($P_{ET}CO_2$) partial pressures were controlled and monitored using a sequential gas delivery breathing circuit and a prospective, feed-forward gas delivery system (Respiract™, Thornhill Research Inc., Toronto, Canada). Subjects were visually cued to perform a bilateral sequential finger tapping task of 28.8s ON, 28.8s OFF, with two trials being performed at both normoxia and hyperoxia (Fig. 1a,b). Normoxia was targeted at the subject's resting value ($P_{ET}O_2$ ~100 mmHg) and hyperoxia at 500 mmHg $P_{ET}O_2$. Isocapnia was maintained throughout at the subject's resting value ($P_{ET}CO_2$ ~40 mmHg). Gradient-echo EPI data (TE=25ms, SENSE 3, voxel band-width=41.5Hz, 20 axial slices of 2 mm isotropic voxels spanning the motor cortex, TR=2.4s) were acquired throughout the hyperoxia task. In 3 subjects, an additional finger tapping task of 10 repeats of 30s ON, 30s OFF was performed during an ASL acquisition (FAIR, TI= 1400ms, TE=14ms, 8 slices 2x2x4mm^3, TR=3s (6s for a tag/control pair); selective thickness 10mm wider than imaging volume; non-selective thickness 300mm; background suppression pulses at 402 and 639ms; in-plane pre- and post-saturation) and an M_0 image was acquired following ASL. BOLD datasets were motion corrected (MCFLIRT, FSL, Oxford, UK) and linear detrended. ROIs were defined from clusters significantly activated by the motor task (Z>5, cluster P(0.05), FEAT, FSL). Voxelwise normalisation to the normoxic baseline was performed (Fig. 1a), and the signal timecourses averaged over the active ROI formed. Active and rest signals at hyperoxia and normoxia were estimated, and the % change of these signals calculated relative to normoxia. % change was then converted to ΔR_2*, $\Delta R_2* \approx -(S/S_0-1)/TE$ (S_o=normoxic baseline), and these values used in a linear regression against (1-q_h) (Fig. 1d). Standard ASL analysis was performed.

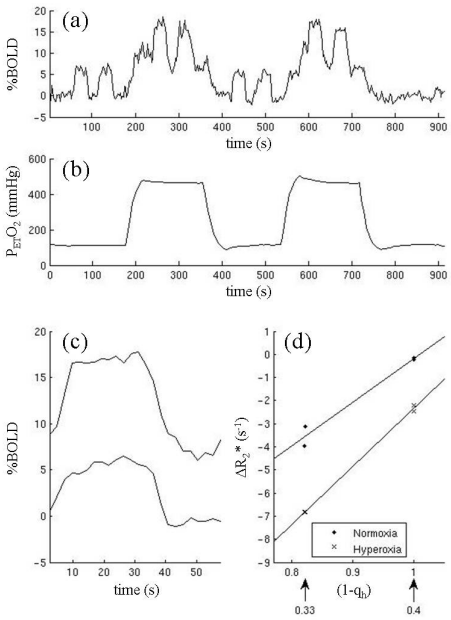

Figure 1: Single subject (a) %BOLD timecourse, relative to normoxic baseline; (b) $P_{ET}O_2$ trace; (c) average finger tap trial %BOLD for hyperoxia (above) and normoxia (below) periods; (d) linear regression, where the numbered arrows indicate the [dHb] fraction at that point.

Results: Representative BOLD and $P_{ET}O_2$ timecourses for a single subject are shown in Fig. 1(a,b). The BOLD signal change to hyperoxia was 7±1%. A signal drift was observed during hyperoxic periods, which was not present during normoxic periods (Fig 1a). To prevent this causing overestimation in the fitted values, only the first finger tap in each hyperoxic period and the immediately preceding normoxic finger tap trial were used. The BOLD signal change to the motor task increased by a factor of 41±8% (mean±SEM over subjects) at hyperoxia, compared to normoxia (e.g. Fig. 1c). The relative increase in *vCBV* (ratio of gradients) during the motor task, relative decrease in q_{act}, and corresponding decrease in [*dHb*] fraction are shown in Table 1. For the 3 participants with ASL measurements, CBF increased by 44±9%, using Fick's Principle (1) giving a relative change in $CMRO_2$ of 30±6%.

Subject #	vCBVact (%)	q_act (%)	Δ[dHb]	CMRO2act (%)
1	36.8	-36.9	-0.15	
2	23.6	-56.1	-0.22	
3	33.3	-33.6	-0.13	
4	33.7	-39.9	-0.16	
5	30.5	-32.2	-0.13	24.1
6	32.1	-30.9	-0.12	25.4
7	30.7	-35.2	-0.14	41.6
mean±SEM	32 ± 2	38 ± 3	0.15 ± 0.01	30 ± 6

Table 1: Relative changes in parameters for subjects.

Discussion: A new method for measuring venous blood volume, oxygenation and $CMRO_2$ changes on neuronal activation has been presented. This method requires no knowledge of the coupling constant (α) between CBF and *vCBV*. Previous studies used an assumed value of Grubb's constant, but this is poorly characterised and likely to vary between brain regions and subjects. $CMRO_2$ changes measured here agree with previous studies using a motor task (9). The use of isocapnia was essential for the assumption that there is no change in blood volume due to hyperoxia, and $P_{ET}CO_2$ was maintained to within ± 1mmHg. An unexpected signal drift was observed during hyperoxic periods, which will be the subject of future investigations. In future studies we plan to implement a combined ASL/R_2* measurement (10), for simultaneous, rather than sequential CBF measures. The theory described here assumes a linear relationship between blood susceptibility and R_2*, which has been confirmed at 7T using graded hypercapnia (8). However, the method could be adapted for a supra-linear relationship for application at lower fields.

References: (1) Davis, PNAS 95:1834, 1998; (2) Chiarelli, NeuroImage 37:808, 2007; (3) Grubb, Stroke 5:630, 1974; (4) Rostrup, NMR in Biomed. 8:41, 1995; (5) Bulte, JMRI 26:894, 2007; (6) Blockley, Proc. ISMRM 18:3476, 2010; (7) Yablonskiy, MRM 32: 749, 1994; (8) Driver, NeuroImage 51:274, 2010; (9) Chiarelli, Mag. Res. In Med. 57:538, 2007; (10) Wesolowski, Proc. ISMRM 17:6132; 2009. **Acknowledgement:** Funded by the UK Medical Research Council