Can the calibrated BOLD scaling factor M be estimated just from R_2' in the baseline state without administering gases?

N. P. Blockley[1], V. E. Griffeth[1], and R. B. Buxton[1]
[1]Center for fMRI, Department of Radiology, University of California San Diego, La Jolla, California, United States

Introduction – The calibrated BOLD method is a powerful tool to measure changes in the rate of oxidative metabolism ($CMRO_2$) during brain stimulation (1). However, this method requires a calibration experiment to determine the local scaling parameter M that defines the maximum BOLD signal if all deoxyhaemoglobin was removed. This calibration step, using a hypercapnic or hyperoxic respiratory challenge, is time consuming to perform and can be uncomfortable for the participant, limiting its widespread use. An alternative approach has been proposed for measuring steady state $CMRO_2$ using an asymmetric spin echo (ASE) to examine properties of the transverse signal decay (2). However, this method relies on a complex model and requires knowledge of underlying factors such as vessel geometry and haematocrit. In this work we consider a hybrid possibility: estimating M for the calibrated BOLD method from a measurement of R_2' in the baseline state using an ASE sequence, eliminating the need for a respiratory challenge. The key question is: what fraction of the ΔR_2^* change with activation is captured by R_2' in the baseline state?

Theory – The calibrated BOLD method is based on a model of the physiological components of the BOLD signal (Eq. 1). For a purely extravascular signal model, changes in R_2^* are caused by dephasing of tissue spins in the magnetic field offsets caused by deoxygenated blood vessels. For static spins, this signal decay is recoverable and can be measured as R_2' using an ASE. This R_2' value can then be used to calculate the maximum BOLD signal change with $M=TE\cdot R_2'$. In reality diffusion of the spins causes incomplete refocusing of this decay that is dependent on the vessel diameter (3). Monte Carlo simulations at 1.5T (3) suggest that an ASE with TE=40ms would measure 72% of the extravascular ΔR_2^* around capillaries (r=3μm) and >97% of the change around large vessels (r=10μm). Assuming a 1:1 ratio of small:large vessels (4), 85% of ΔR_2^* is measured by this method. However, this neglects intravascular signal where the degree of unrecoverable decay is much greater. The contribution of this signal to M can be defined by calculating the ΔR_2^* between a 60% resting oxygenation and full oxygenation. Based on measurements of blood R_2 and R_2^* we estimate that ASE measures 45% of this difference (5). Finally by combining the intravascular and extravascular contributions as 40% and 60% of the total (6), we estimate that ASE captures ~69% of the baseline signal decay that underlies M. This fraction can be increased further by applying flow weighting to crush signal originating in the macrovasculature. Assuming this affects approximately half of the blood volume then this fraction could rise to ~75%. A further consideration when measuring R_2' is the presence of magnetic field inhomogeneity which will cause an increase in R_2' and hence M.

$$\frac{\Delta S}{S_0} = M\left[1-\left(\frac{CBF}{CBF_0}\right)^{\alpha-\beta}\left(\frac{CMRO_2}{CMRO_{20}}\right)^{\beta}\right] \quad [1]$$

Method – A feasibility study was performed to compare this new ASE method with hypercapnia calibration. Single shot spiral images were acquired using a GE Signa HDx 3T (GE Healthcare, Waukesha, WI) with the following parameters; FOV 256mm, 64x64 matrix, five 6mm slices. ASE data were acquired with TE 40ms, TR 5s, reps 10 and τ ranging from 20ms to 40ms in 2ms steps, where $\tau/2$ is the time shift of the 180° pulse. Hypercapnic calibration was performed using 2 runs of a 2min air – 3min 5% CO_2 -2min air paradigm. Images were acquired with PICORE QUIPPSII (8); TI_1 700ms, TI_2 1400ms, TE 9.8/30ms, TR 2s, reps 210. Subjects were instructed to fixate on a point during both calibration experiments. ROIs were defined from a functional experiment using the same ASL parameters (reps 190). Stimulus consisted of 2 runs of 4 cycles of a flickering checkerboard (20s on - 60s off). Data was extracted using this functional ROI in order to calculate M. For the hypercapnia calibration α and β were defined as 0.21 and 1.3, respectively (8). These values are based on venous CBV measurements and optimised for 3T. These values are not required for ASE calibration as they are incorporated in the measurement of M. High resolution field maps were not acquired but correction for magnetic field inhomogeneity was performed assuming a typical gradient of 10Hz (2), reducing the measured R_2' by ~15%. Flow weighting was applied in ASE and ASL experiments (b=2s/mm^2) to reduce the intravascular signal contribution.

Results & Discussion – Table 1 lists the measured calibration values for the ASE (M_{ASE}) and hypercapnia (M_{HC}) methods. Mean M_{ASE} was ~77% of M_{HC}, in good agreement with the rough theoretical estimates above. For M_{ASE} it is known that ASE cannot capture all of the signal underlying M due to irreversible decay, but it is possible a correction could be performed if this is a stable ratio for different vessel distributions and physiological states. To test this requires detailed modeling to accurately estimate this correction factor and determine its variation amongst the subject population. In addition, correction for the through slice gradient contribution to R_2' can be done for each subject using a high resolution field map. Flow weighting was used to reduce the intravascular signal contribution. Further investigation is needed to determine the optimal level of weighting and estimate the systematic error involved. In conclusion, the ASE sequence shows promise as a means of calibrating the BOLD response without administering any gases, avoiding concerns about whether these gases alter metabolism, and widening the application of calibrated BOLD.

Subj.	M_{HC} (%)	M_{ASE} (%)
1	6.0	4.6
2	4.6	4.1
3	7.4	5.1
Mean±SD	6.0±1.4	4.6±0.5

Table 1 – Calibration constants for hypercapnia (M_{HC}) and ASE (M_{ASE}).

References – (1) Davis *et al*., PNAS, 95:1834 (1998), (2) An & Lin, MRM, 50:708 (2003), (3) Boxerman *et al*., MRM, 34:555 (1995), (4) Weber *et al*., Cereb Cortex, 18:2318 (2008), (5) Zhao *et al*., MRM, 58:592 (2007), (6) Driver *et al*., Proc ISMRM, #3478 (2010), (7) Wong *et al*., MRM, 39:702 (1998), (8) Mark *et al*., Neuroimage, In Press, (2010).
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