Measurement of absolute $CMRO_2$ by simultaneous hypercapnic and hyperoxic calibration of FMRI signal

Richard G Wise[1], Ashley D Harris[1], Alan J Stone[1], and Kevin Murphy[1]
[1]*CUBRIC, School of Psychology, Cardiff University, Cardiff, United Kingdom*

Target audience. Researchers and clinicians interested in quantitative FMRI to measure absolute cerebral oxygen metabolism.

Purpose. MR methods have begun to emerge using a calibrated FMRI approach to estimate absolute $CMRO_2$[1,2] and may have the potential to replace the radiotracer-based ^{15}O PET. These methods use both hypercapnia and hyperoxia induced CBF and BOLD signal changes to estimate venous deoxyhaemoglobin concentration [dHb] and thus oxygen extraction fraction (OEF) and absolute $CMRO_2$. They have so far used pre-set inspired concentrations of O_2 and CO_2 to induce hypercapnia and hyperoxia. We present an alternative, time-efficient experimental design in which end-tidal partial pressures of O_2 and CO_2 are targeted to induce hyperoxia during multiple levels of hypercapnia (Fig. 1). A BOLD signal model that combines the effects of hypercapnia and hyperoxia is applied to the data in order to extract not only OEF, but also to estimate key vascular parameters α (the Grubb exponent relates CBF and CBV, eq 2), and β, the exponent relating the relaxation rate R_2* to [dHb]. Previous methods have had to assume literature values for these two parameters.

Methods.

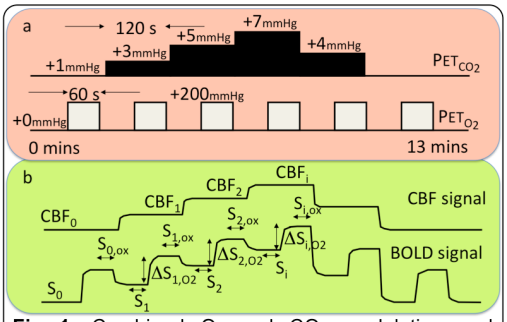

Fig 1. Combined O_2 and CO_2 modulation and schematic of signal changes.

$$\frac{\Delta S}{S_0} = M\left\{1-\left(\frac{CBF}{CBF_0}\right)^{\alpha}\left(\frac{[dHb]}{[dHb]_0}\right)^{\beta}\right\} \text{ eq1} \quad \text{where} \quad \left(\frac{CBV}{CBV_0}\right)=\left(\frac{CBF}{CBF_0}\right)^{\alpha}, \text{ eq2} \quad M = TE\cdot A\cdot CBV_0\cdot[dHb]_0^{\beta} \text{ eq3}$$

$$\text{and} \quad \frac{[dHb]}{[dHb]_0}=\frac{CBF_0}{CBF}-\frac{1}{[dHb]_0}\left\{\frac{1}{\phi}\left(CaO_2-\left(\frac{CBF_0}{CBF}\right)CaO_2|_0\right)+[Hb]\left(\frac{CBF_0}{CBF}-1\right)\right\} \text{ eq4}$$

$$CMRO_2 = CaO_2\cdot OEF\cdot CBF \text{ eq5}$$

Fig 2. Simplified BOLD signal model yielding $[dHb]_0$ (thus OEF & absolute $CMRO_2$), M, α & β. Subscript '0' denotes baseline. $\Delta S/S_0$=fractional BOLD signal change; M=max. BOLD signal change; [dHb]=blood deoxyhaemoglobin concentration; CBF=cerebral blood flow; CBV=cerebral blood volume (principally venous); α='Grubb' exponent; β=exponent relating R2* to [dHb];[Hb]=haemoglobin concentration (assumed 15 g Hb dL^{-1}_{blood}, but can be measured); $\phi=O_2$ carrying capacity of haemoglobin (1.34 mlO_2/g_{Hb}); CaO_2=arterial oxygen content (calculated from PaO_2); OEF=oxygen extraction fraction (calculated from $CaO_2|_0$ and $[dHb]_0$). *Principal assumptions*: extravascular BOLD; isometabolic changes in CaO_2 and CBF

Eleven subjects (5 female, age: 29±5.3 years) were scanned at rest while respiratory challenges were administered for 13 mins (Fig 1) using a system of dynamic end-tidal forcing[3]. Images were acquired on a 3T MRI system (GE Excite HDx) using a PICORE QUIPSS II ASL[4] sequence with dual-echo gradient echo spiral readout (TE_1=3 ms TE_2=29 ms, TR = 2.2s, FOV 22 cm, matrix 64x64, 10 slices of 7mm thickness with an inter-slice gap of 1 mm, TI_1=700 ms, TI_2=1600 ms for the most proximal slice, 354 image volumes). The first echo data were used to calculate CBF, while those from the second echo were used to quantify changes in T_2* weighted signal. A Bayesian framework was used to fit the model expressed in eqs.1,2 and 4 (Fig 2) to the data (for anatomical regions of interest and voxel-wise within grey matter only) to yield M and SvO_2 permitting calculation of absolute $CMRO_2$ when combined with CBF. Priors for M, SvO_2, α and β were normal probability density functions (means= 0.08, 0.5, 0.3 and 1.4; and SD= 0.02, 0.1, 0.1 and 0.2 respectively). Subjects' voxels/ROIs were excluded if one or more of the variables were estimated to be at the boundary of its integration range.

Results

Region	CBF ml/100g/min	M	SvO_2	$CMRO_2$ µmol/100g /min	α	β	#sub/ 11
Occiptal	65.3 ± 17.0	0.078 ± 0.014	0.55 ± 0.11	239 ± 77	0.32 ± 0.05	1.34 ± 0.12	11
Thalamus	60.7 ± 13.6	0.082 ± 0.011	0.61 ± 0.11	193 ± 60	0.35 ± 0.05	1.28 ± 0.16	11
ACC	54.5 ± 15.3	0.077 ± 0.019	0.57 ± 0.12	185 ± 61	0.32 ± 0.05	1.37 ± 0.13	11
Frontal	46.9 ± 14.4	0.071 ± 0.014	0.60 ± 0.11	145 ± 48	0.35 ± 0.04	1.28 ± 0.08	11
Insula	67.4 ± 16.1	0.078 ± 0.017	0.57 ± 0.08	231 ± 49	0.34 ± 0.06	1.31 ± 0.16	9
Parietal	43.4 ± 11.3	0.083 ± 0.011	0.61 ± 0.11	137 ± 45	0.35 ± 0.07	1.29 ± 0.19	9
Grey Matter	55.9 ± 11.6	0.084 ± 0.012	0.58 ± 0.12	184 ± 45	0.33 ± 0.06	1.35 ± 0.13	11

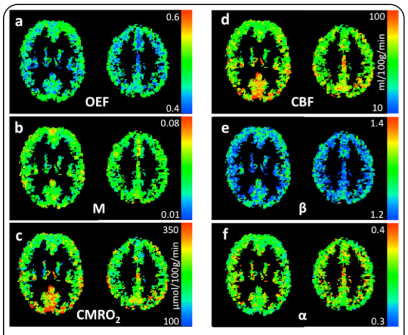

Fig 3. Group mean vascular and metabolic parameters in grey matter only (*n*=11).

Discussion. Our values of absolute $CMRO_2$ in grey matter are consistent with, although slightly higher than, those observed using PET (typically 128-149 µmol /100ml/min[5]). This may result from our estimates of regional CBF, since our OEF estimates are similar to previous reports[5]. Higher $CMRO_2$ in insula and occipital regions is consistent with PET observations[6]. OEF appears spatially uniform. The estimated parameters α and β are consistent with often-quoted values (e.g. 0.38[7] and 1.3-1.5 respectively).

Conclusions. The sensitivity of the hyperoxia induced BOLD signal changes to CBF induced changes in CBV means that our combined approach of intermittent hyperoxia with multiple levels of hypercapnia reduces the assumptions needed in the model used to estimate $CMRO_2$, an advantage over sequential administration of hypercapnia and hyperoxia. Moreover, the 13 min acquisition used here is shorter than other reported paradigms[1,2]. The need for fewer assumptions should expand the range of (patho)physiological conditions in which the method could be applied.

References.

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