Measuring the influence of hypercapnia on absolute $CMRO_2$ in humans

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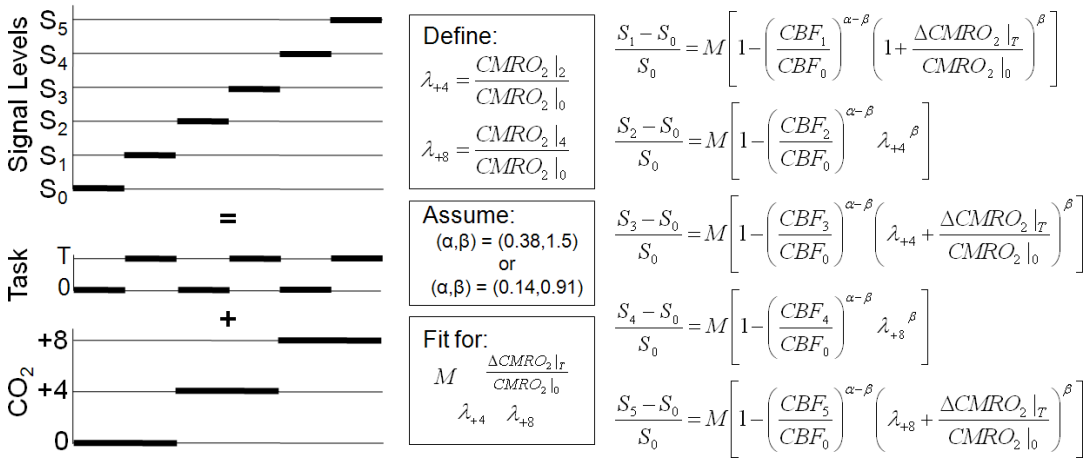
Target audience: Researchers using hypercapnia for calibrated BOLD techniques

Purpose: Hypercapnia induced by CO_2 inhalation is often used in calibrated BOLD techniques to determine the maximum possible BOLD response (usually denoted as *M*) [1,2]. The assumption is that an increase in arterial CO_2 tension which results in an increase in CBF does not affect $CMRO_2$ (cerebral metabolic rate of oxygen). This assumption has been called into question with several studies showing conflicting results including increases [3,4], decreases [4,5] and no change [6] in $CMRO_2$ with hypercapnia. The current study seeks to identify potential changes in absolute $CMRO_2$ at two different levels of hypercapnia compared to normocapnia.

Methods: Fifteen subjects participated in 2 sessions in which scans were acquired at 3T using a PICORE QUIPSS II dual-echo ASL sequence (12 slices, 64 spiral, TE1=3.3ms, TE2=29ms, TR=2200ms, FOV=22cm, slice thickness/gap=7/1mm, TI1=600ms, TI2=1500ms, reps=490). Twenty to 30s blocks of fingertapping and visual task were presented whilst end-tidal CO_2 levels were changed at 2 minute intervals between baseline, +4mmHg and +8mmHg values. CBF time series were calculated from the first echo by separating tag and control time series, interpolating to the TR and subtracting. A similar procedure using averaging rather than subtraction yielded BOLD time series from the second echo. The resulting time series were averaged over visual and motor cortex grey matter voxels for each subject and session. The time series were down-sampled by averaging over the last 15s of each rest and task period. The model in Fig. 1 was fit to the data using a non-linear fitting routine. In the model the change in $CMRO_2$ due to the task was assumed to be the same for all CO_2 levels and the ratios λ_{+4} and λ_{+8} represent the change in absolute $CMRO_2$ from baseline levels for the +4mmHg and +8mmHg CO_2 conditions. Repeatability between the sessions was calculated with intra-class correlation coefficients (ICC).

Figure 1: Model to determine $CMRO_2$ change with hypercapnia



Results: The ratios of $CMRO_2$ changes to baseline levels during hypercapnia are shown for both the motor (Table 1) and visual (Table 2) cortices. Results are shown for the traditional (α,β) pairing of (0.38,1.5) [1,2] (although similar results were found for a newly proposed optimised pairing (0.14,0.91) [8]). Subjects that reached the boundary conditions of the non-linear fitting routine were removed from the averages. For +4mmHg condition in the motor cortex, the ratio λ_{+4}, although found to repeatable between sessions (ICC =0.647), did not differ significantly from 1. A similar non-significant results was found in the visual cortex for the +4mmHg condition. $CMRO_2$ was found to significantly decrease in the motor cortex in the +8mmHg condition (see λ_{+8} column in Table 1), a highly repeatable result between the sessions (ICC=0.706). Averaging across the sessions, a reduction of ~8% in absolute $CMRO_2$ in the motor cortex was observed. A trend towards lower $CMRO_2$ in the +8mmHg condition can also be seen in the visual cortex but the result did not reach significance.

Discussion: The proposed model demonstrates that changes in absolute $CMRO_2$ during hypercapnia can be measured directly from simultaneously acquired BOLD and ASL data. The results show that for the lower CO_2 challenge of +4mmHg, absolute $CMRO_2$ does not significantly differ from baseline. This is in agreement with previous recommendations regarding suitable hypercapnic levels for calibrated BOLD [9]. Decreases in $CMRO_2$ from baseline are observed in the +8mmHg, although not as large as the 13-15% previously reported [5,6]. Differences between the motor and visual cortex results suggest that some brain regions may be more susceptible to $CMRO_2$ changes during hypercapnia than others.

Table 1

Motor	λ_{+4}	λ_{+8}	#subs	(α,β)
Sess1	1.01±0.08 (p=0.748)	0.93±0.08 (p=0.036)	9/15	(0.38,1.5)
Sess2	0.98±0.10 (p=0.508)	0.92±0.10 (p=0.016)	10/15	
ICC	0.647	0.706	7/15	

Table 2

Visual	λ_{+4}	λ_{+8}	#subs	(α,β)
Sess1	1.03±0.08 (p=0.309)	0.99±0.11 (p=0.676)	12/15	(0.38,1.5)
Sess2	0.97±0.07 (p=0.141)	0.93±0.09 (p=0.045)	11/15	
ICC	0.298	0.429	9/15	

Conclusions: By modelling absolute $CMRO_2$ changes during hypercapnia, decreases were observed but only for the +8mmHg condition. This roughly corresponds to a 5% CO_2 challenge, a concentration regularly used in the calibrated BOLD literature. These results suggest that a lower level of hypercapnia (~4mmHg) must be used for the assumptions of calibrated BOLD to hold.

References: [1] Davis (1998) PNAS 95:1834; [2] Hoge (1999) PNAS 96:9403; [3] Hovarth (1994) JCBFM:14,503; [4] Jones (2005) NI:27,609; [5] Xu (2011) JCBFM:31,58; [6] Zappe (2008) CC:18,2666; [7] Chen (2010) JCBFM:30,1094; [8] Griffeth (2011) NI:58,198; [9] Hoge (2012) NI:62,930
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