Time-Related Flow-Metabolism Relationship in Activated Human Visual Cortex: fMRI vs. PET

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Introduction: The change in $CMRO_2$ ($\Delta CMRO_2$) as well as its relationship with the changes in cerebral blood flow (ΔCBF) during neuronal activation has been extensively studied using PET and fMRI. Using PET, Mintun et al. (1) demonstrated a negative correlated relationship between $\Delta CMRO_2$ and ΔCBF ($\Delta CMRO_2$ appeared to rise while ΔCBF tended to decline) during prolonged visual stimulation (25 min). In contrast, by using a BOLD-based fMRI model, Hoge and his co-workers (2) found that the ΔCBF and $\Delta CMRO_2$ were positive linearly coupled. As a consequence, the prediction of $\Delta CMRO_2$ over time using fMRI is conflict with the observation by using PET. In a previous rate-dependence PET and fMRI study (3), we have demonstrated that the traditional fMRI model (2) was oversimplified and that may cause considerable errors for determining the $\Delta CMRO_2$. In the present study, we hypothesize that the apparent disagreement in the time response of $\Delta CMRO_2$ and ΔCBF can be resolved by using an improved fMRI model (3). We performed a prolonged (21 min) visual fMRI study. The $CMRO_2$ changes as well as relationship between CBF and $CMRO_2$ was evaluated by both the original BOLD-based and its improved fMRI models. The results from this fMRI study were further compared with those obtained from Mintun's PET results.

Methods: Experiments were performed on a 3T Siemens Trio MRI scanner. Eight healthy volunteers participated in this study. Visual stimulation was performed using a black-white checkerboard reversing its contrast at 8 Hz. The visual stimulation paradigm consisted of 3-min baseline (resting state) followed by a 21-min visual stimulus. A single oblique axial slice (6 mm in thickness) encompassing the primary visual cortex was chosen for functional imaging. Pixel size was 4.1 × 4.1 mm^2. EPI sequence was used with TR of 2 s and TE of 9.4, 11.6, and 28.1 ms for VASO, ASL, and BOLD images, respectively. Inversion slab thickness was 100 mm. TI_1 (blood nulling point) was determined empirically by searching for minimal signal intensity of the sagittal sinus area in the inversion recovery sequence (~534 ms), and TI_2 was 1200 ms. During an inversion recovery cycle, three images sensitive to VASO, ASL, and BOLD, respectively, were collected (4).

Data Analysis: The VASO image series was obtained by adding the adjacent slab-selective and nonselective images acquired from the first echo in the inversion recovery sequence. The ASL/BOLD image series was obtained by subtracting/adding the adjacent slab-selective and nonselective images from the second/ third echo in the sequence. The images (VASO, ASL and BOLD) acquired during the visual activation will be treated as activation images and will be divided by 4 time periods from 0 to 3, 6 to 9, 12 to 15 and 18 to 21 min, respectively. An additional period (3-6 min) was analyzed in order to exam the turning points of ΔCBF, $\Delta CMRO_2$ and $\Delta BOLD$. Student's *t* tests were used to compare "baseline" and "stimulus" signals. Threshold was set to $t = 3.0$ ($P < 0.005$). Only the common activation pixels that passed the statistically significant threshold for all the VASO, ASL, and BOLD functional maps were utilized for calculating average of the signal changes of the CBV, CBF, and BOLD, respectively.

Original BOLD-based Model (2,3)

Determination of $CMRO_2$ changes

$$\frac{\Delta CMRO_2}{CMRO_{2,0}} = \left(1 - \frac{\left(\frac{\Delta BOLD}{BOLD_0}\right)}{M}\right)^{\frac{1}{\beta}} \cdot \left(1 + \frac{\Delta CBF}{CBF_0}\right)^{1-\frac{\alpha}{\beta}} - 1$$

where α=0.38, β=1.5, M=0.24 was determined by extrapolating from the value of M = 0.22 at 1.5 T (2)

Improved Model (3,5)

Determination of $CMRO_2$ changes

$$\frac{\Delta CMRO_2}{CMRO_{2,0}} = \left(1 + \frac{\Delta OEF}{OEF_0}\right) \cdot \left(1 + \frac{\Delta CBF}{CBF_0}\right) - 1$$

where *OEF* is oxygen extraction fraction.

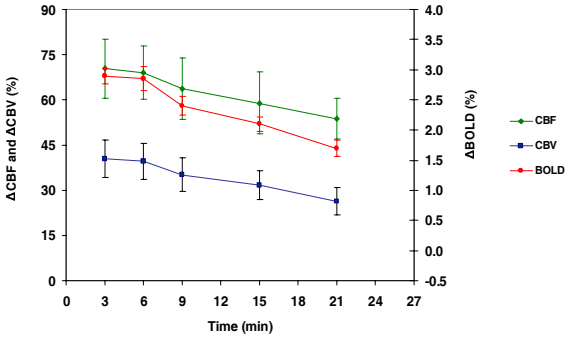

Fig. 1 The average ΔCBF, $\Delta BOLD$ and ΔCBV measured at five stimulus periods

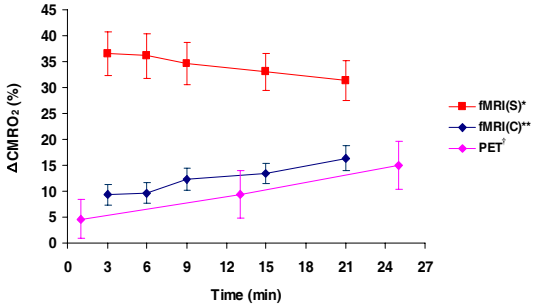

Fig. 2 The $\Delta CMRO_2$ obtained by the original BOLD-based and its improved models at five stimulus periods and their comparison to PET study. * Original BOLD-based model; ** Improved model; † Adapted from ref (1).

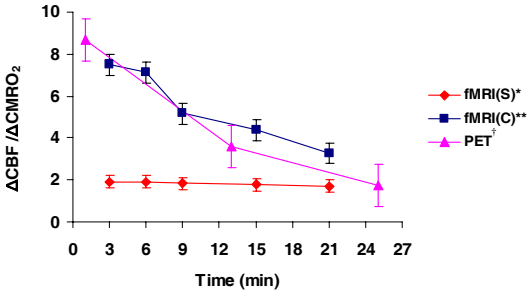

Fig. 3 The flow-metabolism ratio ($\Delta CBF/\Delta CMRO_2$) obtained by the original BOLD-based and its improved models at five stimulus periods and their comparison to PET study (1).

Results and Discussion: The changes in CBV, CBF and BOLD remained constant during at least 6 min of stimulation, and then decreased as the stimulation continued. (Fig. 1). The $\Delta CMRO_2$ generated by the two models also both remained constant during the first 6 min (Fig. 2). However, their values and temporal behavior during continued activation was significant different. The average $\Delta CMRO_2$ obtained by the original BOLD-based model tended to decline as the stimulation continued, from 36.6 % at beginning (0 min) to 31.3% at the end of the stimulation (21 min). In contrast, those obtained by the improved model appeared to increase during prolonged stimulation, from 9.4 to 16.4%. The comparison of the $\Delta CMRO_2$ between the two models was performed using Student's *t* test. As a result, a statistically significant difference was found at all the five stimulation periods between the values determined by the two models ($P < 0.005$). Figs. 2 and 3 demonstrate respectively the comparisons of $\Delta CMRO_2$ and flow-metabolism coupling ratio between two fMRI models and PET literature results (1). It shows that with the elimination of the inappropriate assumptions that had been used in the original BOLD-based model, the magnitude and the pattern of $\Delta CMRO_2$ over time during the prolonged visual stimulation calculated by the improved fMRI model were in good agreement with PET results (1). The increase of $\Delta CMRO_2$ suggests that energy demands of prolonged neuronal activation eventually require increased oxidative metabolism. The decrease of ΔCBF could be due to the decrease of lactate/pyruvate ratio (lactate is the end product of anaerobic glycolysis) (6). The results imply that $\Delta CMRO_2$ would not necessary associate with ΔCBF during neuronal activity.

References: (1) Mintun et al., *NeuroImage* 2002; 16:531-537. (2) Hoge et al., *MRM* 1999; 42:849-863. (3) Lin et al., *Proc ISMRM*, 2006; 14:539. (4) Yang et al., *MRM* 2004; 52:1407–1417. (5) Lu et al., *JCBFM* 2004; 24:764-770. (6) Mintun et al., *PNAS* 2004; 101:659-664.