Decrease of Deoxy-Hemoglobin Containing Blood Volume in Activated Human Visual Cortex

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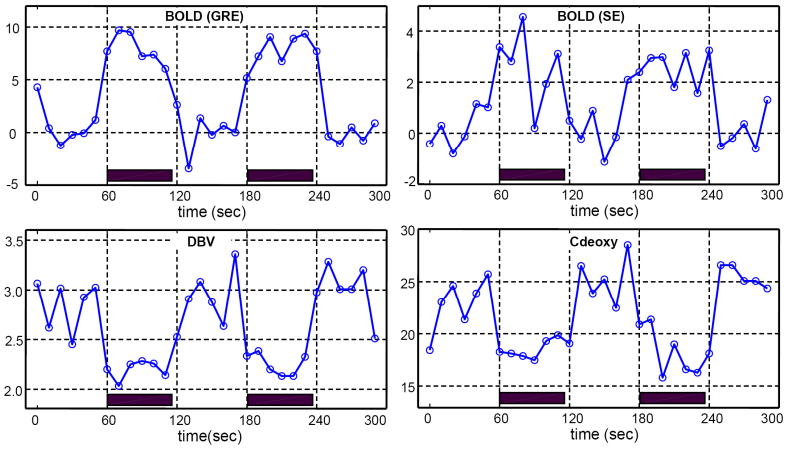
Introduction: Quantification of brain hemodynamic parameter such as cerebral oxygen extraction fraction (OEF), cerebral blood volume (CBV), cerebral blood flow (CBF) and cerebral metabolic rate of oxygen (CMRO2) during functional activation is essential for understanding of the biophysical mechanisms defining blood oxygenation level depend (BOLD) phenomenon. Even after decades of investigation using PET [1] and MRI [2], the origins of functional BOLD signal are still under intense debate. In most BOLD models changes in CBV and its relation to changes in CBF established from PET studies are used to account for BOLD signal changes. However, only part of CBV, specifically veins and pre-venous portion of capillaries - Deoxy-hemoglobin containing Blood Volume (DBV) - create magnetic field inhomogeneities around themselves, inducing the BOLD-related changes of tissue transverse relaxivity. Previously proposed [3, 4] and validated [5] quantitative BOLD (qBOLD) model offers means to directly measure DBV and blood oxygenation level. In this study, we measured these hemodynamic parameters during visual activation in human primary visual cortex area using qBOLD-fMRI technique. We demonstrate for the first time that DBV *decreases* during functional activation – the effect opposite to well known *increase* in CBV.

Methods: Six healthy volunteers were recruited for this study. All images were acquired on a Siemens 3.0 Trio whole body scanner with a 12 channel receive-only head coil. 2D single slice Gradient Echo Sampling of Spin Echo (GESSE) sequence [3, 4], which acquires 71 gradient echoes with echo train spacing of 2.36 *ms* and spin echo at 10th echo corresponding to 68 *ms*, spatial resolution of 4x4x8 *mm*^{3}, TR of 200 *ms*, sampling matrix of 64x48 was used allowing temporal resolution about 10 seconds. The initial activated visual cortex area was determined from a separate EPI BOLD experiment and GESSE slice was positioned to cover activated area. To compensate for MR signal decay due to macroscopic field inhomogenieties, a high resolution 3D field map (1x1x2 *mm*^{3}) was acquired with T_R 25 *ms*, TE of 4.92 and 12.33 *ms*. Visual stimulation was achieved with a black-and-white flashing checker board pattern with a stationary cross at the center. Volunteers were instructed to focus on the center cross during the entire fMRI study.

Based on qBOLD model [3], the MR signal was analyzed as a sum of signals from intravascular blood, interstitial fluid, and cellular/tissue compartments. The latter is $S_{tissue} = \exp\left(-R2_{tissue} \cdot t - DBV \cdot f_c\left(\delta\omega \cdot t\right)\right)$ [6]. Where f_c is a function defining contribution of blood vessel network to the tissue MR signal decay, $\delta\omega = 4/3 \cdot \pi \cdot \gamma \cdot \Delta\chi_0 \cdot Hct \cdot (1-Y) \cdot B_0$, B_0 is the external magnetic field, $\Delta\chi_0$ is the susceptibility difference between completely deoxygenated and completely oxygenated red blood cells (0.27ppm [7]), Hct – blood hematocrit, Y is blood oxygenation level. Parameters DBV and $\delta\omega$ can be estimated by fitting qBOLD model to experimental data. Then tissue concentration of deoxyhemoglobin (dHb) can be estimated as: $C_{deoxy} = DBV \cdot \delta\omega \cdot n_{Hb} \cdot (4/3 \cdot \pi \cdot \gamma \cdot \Delta\chi_0 \cdot B_0)^{-1}$, where n_{HB} is the total intracellular Hb concentration, $5.5^{x}10^{-6}$ *mol/ML*.

Results: Main results are shown in the figure for a typical qBOLD-fMRI study with 60 second ON (black bar) and 60 second OFF activation pattern. Data are from the ROI covering 18 activated voxels identified by a standard fMRI analysis of GRE BOLD time series. Graphs of BOLD (GRE) and BOLD (SE) show relative changes of BOLD signal (in %) acquired with GESSE sequence at 35 ms after spin echo; and at spin echo correspondingly. A robust GRE BOLD activation (about 8%) can be observed in this study.



The second row in the figure illustrates the corresponding absolute measurement of DBV (% of tissue volume) and tissue dHb concentration (*μM*). While each voxel was processed independently, the profiles, as shown, were averaged across 18 activated voxels. Figure demonstrates robust changes during activation of DBV (decrease about 20%) and tissue dHb concentration (decrease about 22%). The amount of dHb decrease during activation (about 5 *μM*) is in-line with NIRS studies.

Discussion & Conclusion: In this study, a significant decrease of DBV in visual cortex area during visual stimulation has been detected by qBOLD-fMRI technique. This result is contrary to the popular assumption that this value increases during functional activation following increase in CBF (see for example [8]). However, recent work [9] did point out that the total blood volume increase during activation can be attributed to the volume increase of the arterial blood. The results found in our study are consistent with the following scenario: Arteries and initial part of post-arterial capillaries carry oxygenated blood, while veins and pre-venous part of capillary bed contain deoxygenated blood - DBV. The increase of CBF during activation may push the oxygenated blood deeper into the pre-venous part of capillary bed, thus reducing the volume occupied by the deoxygenated blood (DBV) and consequently reducing total tissue dHb concentration.

References: **1.** Fox, P.T. and M.E. Raichle, PNAS 1986. 83: p1140; **2.** Ogawa, S., et al., PNAS 1990. 87:p9868; **3.** He, X. and D.A. Yablonskiy, MRM 2007. 57: p115; **4.** Yablonskiy, D.A., MRM 1998. 39: p.417; **5.** He, X. et al, MRM 2008. 60: p882; **6.** Yablonskiy, D.A. and E.M. Haacke, MRM 1994. 32: p749; **7.** Spees, W.M., et al., MRM 2001. 45: p533; **8.** Buxton, R.B., et al., MRM 1998. 39: p855; **9.** Kim, T., et al., JCBFM 2007. 27: p1235.