Plausibility of delayed arteriolar compliance as cause of the BOLD post-stimulus undershoot in presence of post-stimulus elevation in CMRO2: The arterial balloon model

B. A. Poser[1,2], and D. G. Norris[1,2]

[1]FC Donders Centre for Cognitive Neuroimaging, Radboud University, Nijmegen, Netherlands, [2]Erwin L Hahn Institute for Magnetic Resonance Imaging, University Duisburg-Essen, Essen, Germany

Introduction and Theory

Upon neuronal stimulation the MR signal as measured with GE-EPI increases due to the blood-oxygenation level dependent (BOLD) effect. After stimulus cessation this is typically followed by the post-stimulus undershoot below baseline signal which can last for 40-60s. In recent years this effect has reattracted great interest as it may yield insight into cerebral metabolic and hemodynamic processes. Various hypotheses for the undershoot can be found in the literature; these are: **(a)** delayed vascular compliance in the venous compartment, e.g. Balloon model, [1, 2] which after baseline return of $CMRO_2$ and CBF results in static dephasing effects and causes the post-stimulus undershoot in the GE signal, **(b)** sustained $CMRO_2$ after return of CBV and CBV to baseline (Lu et al 2004) and **(c)** CBV changes in the capillary bed [3-5]. Using spin-echo techniques [6] we have previously presented data that reject hypothesis (a), and further show that (c) alone cannot explain the undershoot. Instead the data contained strong evidence that continued oxygen consumption (a) is the dominant contributor [7]. However, under the hypothesis that CBV and CBF return to baseline quickly and simultaneously while $CMRO_2$ remains elevated, one would expect a rapid rise in deoxy-hemoglobin, leading to a fast signal drop into the undershoot. Such a sharp signal decrease however is not typically observed in published data, and from experimental results we estimate that the undershoot 'peaks' approximately 10 – 15 s after stimulus offset. This suggests that the undershoot is delayed by a mechanism that counteracts the $CMRO_2$ related deoxy-hemoglobin accumulation. Identical undershoot-to-peak ratios at 1.5T and 3T [7] moreover indicate that this mechanism has to be field strength independent.

We propose a plausible explanation for the observed timecourse of the BOLD in presence of sustained post-stimulus oxygen metabolism as follows:

A ballooning effect takes place in the arteriolar rather than venous compartment. The consequence of such an arteriolar balloon would be that oxygenated blood flows out of the balloon after stimulus cessation and hence elevates the blood velocity in the capillary bed for some time after the return of blood inflow f_{in} to baseline. Blood outflow f_{out} from the balloon would thus follow f_{in} with some delay that would depend on the vaso-mechanical properties of the arteriolar balloon, in an analogous manner to Buxton et al's venous balloon. The resulting washout would cause a lower deoxy-hemoglobin content in both capillary and venous bed than would have ensued from continued post-stimulus $CMRO_2$ alone, thereby slowing down the transition into the undershoot until the balloon is deflated and the arteriolar diameter has returned to baseline. Convincing evidence for vessel dilation in the arteriolar compartment can be found in the optical imaging literature; [8, 9] for instance report arteriolar (but clearly not venous) diameter changes that agree very well with the measured venous flow speed [8]. This is further underpinned by the results of the recent MR study by Kim et al [4] who find arterial CBV to be by far the main contributor to total blood volume changes.

Methods

To test the plausibility of the 'delayed arteriolar compliance' hypothesis as explanation for the slow transition into the undershoot we constructed an arteriolar balloon by adapting the rate equations of the original Balloon model. The important modifications are (a) the explicit dependence of deoxy-hemoglobin on venous CBV is removed and (b) the outflow from the balloon supplies the capillary bed. The relationship describing the rate of change on CBV remains unaltered. The resulting pair of coupled differential equations is then

$$\frac{dq}{dt} = \frac{1}{\tau_0}\left[CMRO_2(t) - f_{out}(v)\cdot q(t)\right] \text{ and } \frac{dv}{dt} = \frac{1}{\tau_0}\left[f_{in}(t) - f_{out}(v)\right], \text{ where } \quad f_{out}(v) = v^{\frac{1}{\alpha}} + \tau_v \frac{dv}{dt}.$$

In these dimensionless mass equations the dynamic variables $f_{in}(t)$ for inflow into the balloon, $f_{out}(v)$ for outflow from the balloon, $q(t)$ for deoxy-hemoglobin content and $CMRO_2(t)$ are normalized to their baseline values. The constant parameters are the balloon transit time τ_0, the balloon's viscoelastic time constant τ_v which characterizes the time scale for dv/dt, and the Grubb exponent α for the relationship $v=f^{\alpha}$. For the modeling, we assume a baseline oxygen extraction fraction E_0=0.4 and $CMRO_2(t)$ which after offset of a 20 s stimulus either immediately decreases linearly from its plateau value to baseline over the duration of the undershoot (as obtained experimentally by Lu et al [10]) or which remains at the plateau some time longer. The other parameters are set to typical literature values: τ_0=2s, τ_v=6s (estimated from [8]), ramp-up/down time for f_{in} and $CMRO_2$ of 7s, Δf_i =55% and Grubb exponent α=0.4. The modeled $q(t)$ response can directly be compared to the experimentally obtained purely T_2 weighted BOLD curves from [7] (20/40s on/off visual checkerboard stimulation, n=7). As they are proportional to the deoxy-hemoglobin time course, this alleviates the need to determine the weighting parameters necessary for the computation of the GE BOLD signal change, and thereby facilitates a direct comparison with the modeled deoxy-hemoglobin response.

Results and Discussion

For the set of typical model parameters, the deoxy-hemoglobin response predicted by the 'arteriolar balloon model' agrees very well with the experimental data. Fig 1 shows the model input parameters and modeled $q(t)$ for immediately decreasing $CMRO_2$ (top), and $CMRO_2$ that is elevated for an additional 10s before ramping to baseline (bottom). Additional simulations in which τ_0 was varied indicate a balloon transit time of 1.5–2.5s. The model calculations demonstrate the plausibly of a mechanism by which the BOLD undershoot is caused by sustained elevation in $CMRO_2$, and its temporal characteristics are determined by a delayed compliance effect on the *inflow* side. This is in agreement with results from the optical imaging literature.

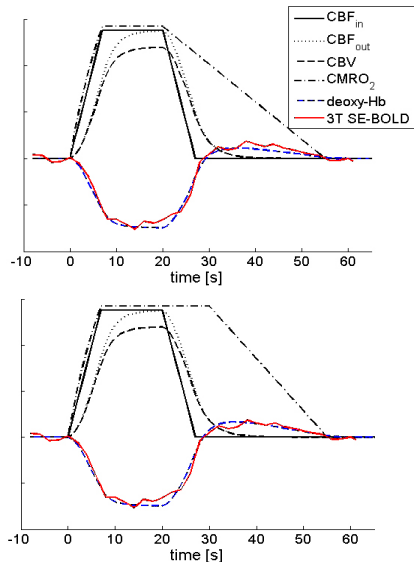

Fig.1 Model predictions for deoxyhemoglobin timecourse (blue) and experimentally obtained T2 weighted BOLD (red)

References

1 .Buxton, R. et al, *MRM*, 1998. **39**(6): p. 855-64.
2 .Mandeville, J. et al., *JCBFM*, 1999. **19**(6): p. 679-89.
3 .Devor, A. et al., Neuron, 2003. **39**(2): p. 353-9.
4 .Kim, T. et al., *JCBFM*, 2007. **27**(6): p. 1235-47.
5. Vanzetta, I..et al J Neurosci,2005. **25**(9): p. 2233-44.
6 .Poser, B.. and Norris D., MAGMA, 2007. **20**(1): p. 11-7.
7 .Poser, B. and D. Norris. *ISMRM*. 2007.
8 .Hillman, E.., et al., Neuroimage, 2007. **35**(1): p. 89-104.
9. Devor, A., et al., J Neurosci, 2007.**27**(16): p. 4452-9.
10. Lu, H.Z., et al., *JCBFM*, 2004. **24**(7): p. 764-770.