On bursting balloons and collapsing endothelia: What does cause the post-stimulus undershoot?

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Introduction and Hypotheses

There are two main hypotheses that provide plausible explanations for the post-stimulus BOLD signal undershoot that is typically observed in GE-EPI fMRI data (1-3); a third model has recently been suggested (4)

We propose that these models can be tested by performing purely T_2 weighted fMRI experiments at field strengths of 1.5T and 3T. At 3T, approximately 50% of the SE-BOLD signal change is intravascular (5), at 1.5T nearly 100%. The occurrence of an undershoot and the ratio of the undershoot to the main BOLD response makes it possible to test the validity of the models using a pure spin echo sequence as follows:

First, the Balloon model family (1,2) according to which a temporal post-stimulus decoupling of cerebral blood flow (CBF) and volume (CBV) –due to "delayed vascular compliance"– causes a relatively slower return of CBV to baseline. The cause of the undershoot would then be extravascular static dephasing (a T_2* effect) that takes place around the larger draining veins. Therefore *no* undershoot should be seen in SE data at *either* field: if the undershoot is a downstream effect, no pronounced dynamic averaging effects should contribute at 3T, and there would be no intravascular signal changes.

The second model postulates an elevated level of post-stimulus oxygen metabolism ($CMRO_2$) (3), based on evidence provided by VASO measurements (6) that show a simultaneous return of CBV and CBF to baseline (3). Sustained oxygen consumption after the return of CBV/CBF to baseline would result in an increased deoxyhemoglobin concentration. The undershoot would then be a 'negative' BOLD effect and would arise from the same contrast mechanisms as the main positive BOLD signal change. Hence an undershoot *should* also be seen in T_2 weighted data at *both* fields. While signal changes at 3T would be expected to be considerably larger than at 1.5T due to the additional contribution of extravascular dynamic averaging effects the ratio of main BOLD effect to undershoot should be constant.

A third mechanism was recently proposed to explain how the typically observed CBV changes are physiologically feasible without concomitant increase in intracranial pressure (4). By this mechanism the endothelium of the venous vessels acts as exchange pool, from which water molecules can diffuse into the intra-capillary space, thereby leading to a volume increase of the blood pool without need for a bulk volume change. The prediction of the Turner-Thomas model is thus that the BOLD undershoot originates in the capillary bed, where the single-layered endothelium accounts for up 20% of the intra-capillary space and acts as a "Windkessel" equivalent. If the collapsing of the endothelium is the only active mechanism and its recovery results in the implied temporal CBV-CBF decoupling, then this means that a dynamic averaging about the capillaries should generate an undershoot at 3T which should be strongly reduced or absent at 1.5T.

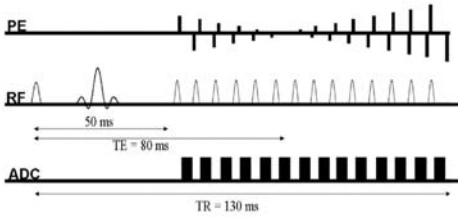

Fig.1 **T_2 weighted HASTE fMRI sequence**

Methods

Experiments were performed on a 1.5T Sonata and 3T TIM Trio (Siemens, Germany), using the product 8-channel (1.5T) and 12-channel (3T) head coils, and a purely T_2-weighted HASTE fMRI sequence as previously described (7). In short, the sequence refocuses the first spin echo at a TE of 50ms to allow for dynamic averaging, followed by a rapid, factor-4 accelerated HASTE readout (Fig.1). The k-space centre is acquired at TE=80ms to optimize sensitivity for the blood signal. Five slices were acquired with a TR of 2s and resolution 3.5x3.5x5mm^3. Measurements of ten minutes duration were made on 7 subjects using 20s on / 40s off checkerboard stimulation. The long rest period was chosen to allow full BOLD signal recovery. Data were reconstructed offline using SENSE. Analysis (motion correction, linear trend removal and t-test) was performed with Brainvoyager 2000 (BrainInnovation, Netherlands). Prior to further analysis, individual response curves were normalized.

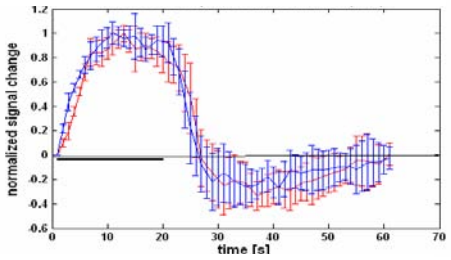

Fig.2 **Stimulus response curves at 1.5T (blue) and 3T (red). Error bars = SD over subjects.**

Results and Discussion

The results are summarized in the table. A significant undershoot is clearly seen in the subject average at both field strengths (Fig.2). Note that there is NO significant difference in the undershoot-to-peak ratio, pointing towards a BOLD mechanism for the undershoot. Our findings thus provide strong evidence for increased oxygen metabolism even *after* the end of stimulation and return of CBV/CBF to baseline, as suggested by Lu et al. It appears that neither Balloon model nor the Turner-Thomas hypothesis provide suitable explanations for the post-stimulus BOLD undershoot, although the latter could very well explain how CBV changes closely follow those of CBF.

Tab 1	undershoot/ peak	% BOLD signal
1.5 T	0.27±0.17	0.95
3.0 T	0.34±0.12	1.71

References

[1] Mandeville JB et al, J Cereb Blood Flow Metab 1999;19(6):679-689;
[2] Buxton RB et al, Magn Reson Med 1998;39(6):855-864;
[3] Lu HZ et al, J Cereb Blood Flow Metab 2004;24(7):764-770;
[4] Turner R and Thomas D., ISMRM, 2006. Abstract 2771;
[5] Norris DG et al, Neuroimage 2002;15(3):719-726;
[6] Lu H et al, Magn Reson Med 2003;50(2):263-274;
[7] Poser BA and Norris DG, Magn Reson Mater Phy, in press.