Origins of the BOLD Post-Stimulus Undershoot

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Introduction

The interpretation of the blood-oxygenation level-dependent (BOLD) signal post-stimulus undershoot has been a topic of considerable interest, as the mechanisms behind this prominent BOLD transient may provide valuable clues on the neurovascular response process and energy supply routes of the brain. The Balloon model [1,2] explains the BOLD undershoot through the purely biomechanical dilation of post-capillary vessels that leads to an increase in venous blood volume (CBV_v), resulting in susceptibility-induced signal decrease. There have been reports countering this theory [3], arguing for a prolonged elevation in cerebral oxygenation consumption ($CMRO_2$) as the primary cause. However, there has also been substantial evidence supporting a definite role for venous ballooning [4-6]. Furthermore, a contribution of post-stimulus cerebral blood flow (CBF) undershoots has been demonstrated [6]. To clarify the role of venous CBV (ΔCBV_v) in causing the BOLD undershoot, we present human *in vivo* fMRI measurements of the transient ΔCBV_v, ΔCBF and $\Delta BOLD$.

Methods

All acquisitions were performed using a Siemens Trio 3T system, involving 20 healthy adult subjects (age = 25.8 ± 2.5 years). The basic imaging parameters were: FOV/matrix/slice-thickness/TR = 200 mm/64x64/5 mm/4 s. Changes in venous cerebral blood volume (ΔCBV_v) were measured using the venous-refocusing for volume-estimation (VERVE) technique, which targets partially deoxygenated blood using the T2 dependence of the latter on the Carr-Purcel-Meiboom-Gill (CPMG) refocusing interval (τ_{180}), and has been demonstrated at 3 Tesla [6]. This study employed a new design of the VERVE sequence based on magnetization preparation and turbo spin-echo readout, as described in another abstract at this meeting. This design eliminates possible T2* contamination, and significantly improves image signal-to-noise ratio. CSF suppression was performed at an inversion time (TI) of 1100 ms, and in the VERVE magnetization preparation, τ_{180} = 3 ms and 24 ms, for fast and slow-refocusing, respectively, to achieve an effective TE of 198.8 ms. The difference between the slow- and the fast-refocused images is ΔVERVE. The calibration from ΔVERVE to ΔCBV_v [4] was performed for each subject using *in vivo* venous blood oxygenation measurements. QUIPSS II arterial-spin labeling (ASL) [9], with scan parameters TI_1/TI_2/TE/labeling thickness/gap = 700 ms/1300 ms/25 ms/100 mm/5 mm, was used to measure ΔCBF (control-tag) and ΔBOLD ((control+tag)/2). Visual activation was induced using an 8 Hz radial yellow/blue checkerboard at 25% and 100% contrast, alternating with a uniform grey field as baseline. Sensorimotor activation was produced through cued bilateral sequential finger tapping at 1.73 Hz and 3.46 Hz. In addition, 2 stimulation-"on" durations were used, namely 24 s and 96 s, each flanked by 16 s and 120 s of pre- and post-stimulus baseline blocks, respectively. Each off/on/off black was repeated twice, and jittered to achieve an effective temporal resolution of 2 s [10]. A 32 s initial baseline was inserted to facilitate resting-state estimation. A 3D T1-weighted scan served as anatomical reference. A functional scout was used for slice positioning.

Acquisition timing differences between control and tag images, as well as between fast- and slow-refocused CBV images, were corrected by *sinc* interpolation. The region-of-interest (ROI) was delineated for each subject by thresholding the CBF, CBV_v and BOLD *t*-maps at $P < 0.05$ (corrected for multiple comparisons). The overlap between all 3 sets of ROIs was used to obtain the time courses in the visual (VC) and sensorimotor (SMC) cortices. CBF, CBV_v and BOLD time courses were temporally low-pass-filtered (Hanning, FWHM = 6 s). Piece-wise fitting of the time courses to a double-gamma hemodynamic response function [4] was performed using the unconstrained nonlinear least-square method. The fall time (T_f) of the time courses (the time taken to fall to the half-maximum) were estimated from the modeled time courses. Furthermore, the amplitude (normalized by the positive response amplitude) and duration (FWHM) of the parameterized undershoots, A_{US} and $FWHM_{US}$, were estimated, with correction for the low-pass filter FWHM. The dependence of these parameters on brain region, stimulation intensity and the stimulation-"on" duration was assessed using paired *t*-tests and linear regression.

Results

An example of the acquired and modeled CBV time course from a single subject is shown in Fig. 1a. The group-mean of T_f, A_{US} and $FWHM_{US}$ for all conditions are summarized in Table 1. The ΔCBF and ΔBOLD T_f estimates were statistically indistinguishable ($P = 0.10$) across all stimulus conditions. However, they were both significantly shorter than the ΔCBV_v T_f ($P < 0.05$), which was not dependent on brain region, stimulation duration or intensity. Moreover, in this analysis, the CBV_v T_f was not significantly correlated with the BOLD undershoot amplitude or FWHM, but interestingly, the CBF undershoot amplitude was highly correlated with that of BOLD ($P < 0.001$). A regional difference was found in the BOLD and CBF undershoots, both of which were significantly greater than the CBV_v undershoots ($P < 0.001$). As reflected in Fig. 1b, the normalized average modeled CBV_v shows, for the most part, slow recovery and no undershoots.

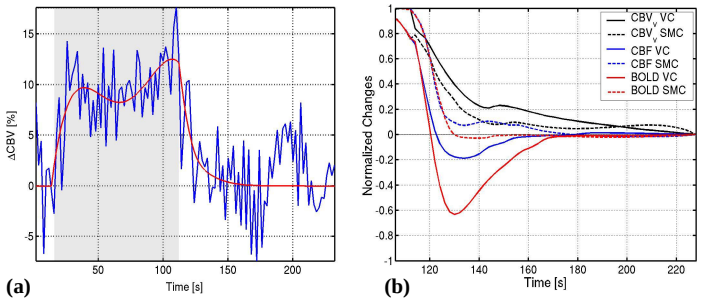

Figure 1. (a) The measured (blue) and modeled (red) ΔCBV_v time courses for 100% visual contrast and a stimulation-"on" duration of 96 s are overlaid, with the shaded regions being the stimulation-"on" time. (b) The post-stimulus segment of the group-averaged modeled CBF, CBV_v and BOLD time courses are shown for the same stimulus condition for the visual (VC) and sensorimotor (SMC) regions.

Conclusion

Using the VERVE technique, we have demonstrated a slow post-stimulus return to baseline of venous CBV in human subjects, which supports the existence of a passive "ballooning" effect described by Buxton et al. [1] and observed in animals by Mandeville et al. and Zhao et al. [4,5]. In this respect, previous observations of a quick recovery of the total CBV response [3] may reflect a dominant arterial component, instead of venous, as was targeted here. Our findings support a biomechanical contribution to the BOLD post-stimulus undershoots [6]. Furthermore, in agreement with previous findings, BOLD and CBF undershoots both varied between visual and sensorimotor stimulation.

mean ± standard error	CBV_v				CBF				BOLD			
	Visual (VC)		Sensorimotor (SMC)		Visual (VC)		Sensorimotor (SMC)		Visual (VC)		Sensorimotor (SMC)	
	25% contrast	100% contrast	1.73 Hz	3.46 Hz	25% contrast	100% contrast	1.73 Hz	3.46 Hz	25% contrast	100% contrast	1.73 Hz	3.46 Hz
T_f (s)	12.5 ± 4.1	9.5 ± 1.8	13.2 ± 9.6	10.7 ± 2.6	3.4 ± 1.0	4.5 ± 0.9	10.0 ± 2.4	6.8 ± 1.2	2.0 ± 0.7	4.0 ± 1.0	10.5 ± 8.3	9.7 ± 3.1
A_{US} (s)	1.1 ± 0.4	1.0 ± 0.5	2.0 ± 1.0	0.9 ± 0.7	10.4 ± 2.6	13.4 ± 1.9	7.1 ± 1.9	6.3 ± 3.2	1.3 ± 0.2	1.9 ± 0.3	0.8 ± 0.3	0.4 ± 0.2
$FWHM_{US}$ (s)	12.0 ± 5.3	5.5 ± 1.9	11.1 ± 4.7	13.8 ± 5.3	24.4 ± 6.7	28.1 ± 7.1	26.2 ± 7.8	9.8 ± 6.3	29.9 ± 4.9	25.2 ± 3.9	17.6 ± 7.8	17.4 ± 9.9

Table 1. The fall time (T_f), undershoot amplitude (A_{US}) and FWHM ($FWHM_{US}$) of the modeled CBF, CBV_v and BOLD data for a stimulus-"on" duration of 96 s

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