Characterization of the BOLD Post-stimulus Undershoot

J. J. Chen[1], K. Advani[1], and G. B. Pike[1]
[1]Montreal Neurological Institute, Montreal, Quebec, Canada

Introduction

The source of the commonly observed post-stimulus BOLD undershoot remains unclear, and various explanations involving the behaviour of cerebral blood flow (CBF) and volume (CBV), as well as oxygen consumption rate ($CMRO_2$), have been proposed, primarily represented by the balloon model [1] and the sustained post-stimulus metabolism theory [2]. The BOLD response can be induced by both neuronal activation and hypercapnic perturbation (HC), and a post-stimulus BOLD undershoot would be expected for both if the relationship between CBF and CBV was purely biomechanical and invariant. Alternatively, if a sustained post-activation elevation of $CMRO_2$ was the sole origin of the undershoot [2], the BOLD undershoot would only be expected after neuronal activation. In addition, the undershoot magnitude and/or duration might be expected to increase with an increasing visual stimulus duration (and be absent following HC), since a sustained post-stimulus $CMRO_2$ increase would presumably occur to restore activation-related energy deficits. Thus, BOLD undershoot magnitudes and durations independent of stimulus duration and type would argue for a biomechanical/hemodynamic origin. In this study, we parameterized the post-stimulus BOLD and CBF undershoots (magnitude and duration) and tested for dependence on stimulus duration and type.

Methods

Two experiments were designed to investigate the source of the post-stimulus BOLD undershoot using a Siemens Trio 3 T and an interleaved BOLD-CBF pulse sequence [3]. Visual activation was induced using a radial yellow/blue checkerboard at 8 Hz contrast reversal, and motor stimulation through finger apposition at 3 Hz. Experiment 1 involved 9 healthy adult subjects (with informed consent), each undergoing 1 session of visual-motor tasks involving 3 repetitions of a 40s/80s/200s off/on/off paradigm, followed by 2 sessions of HC, at 5% and 10%, respectively, using the same timing and number of repetitions. The activated ROIs obtained from BOLD and CBF *t*-maps ($p<0.05$) were segmented based on a T1-weighted 3D anatomical scan to isolate the visual (VC) and the sensorimotor (SMC) cortex. BOLD and CBF undershoots in the overlapping ROIs between the HC and VC or SMC *t*-maps ($p<0.05$) were analyzed. Experiment 2 involved 8 subjects, with 1 to 4 repetitions of visual-motor stimulation, depending on the stimulus "on" time, which were 20, 40, 80 and 120 s, placed between baselines of 40s before and 100s after. The *t*-stat analyses were corrected for multiple comparisons. The overlap between the isolated VC or SMC BOLD and CBF ROI's was selected for analysis. BOLD and CBF time courses were temporally low-pass-filtered (Hanning FWHM=12s) and fit using the nonlinear least-square method to a double-gamma hemodynamic response function [4]. The amplitude and duration (FWHM) of the parameterized undershoots were estimated, with a correction for the low-pass filtering. The dependence of these parameters on HC level and on stimulation duration was assessed using paired *t*-test and single-factor ANOVA.

Results

The BOLD and CBF time courses and the corresponding fits for 1 subject are shown in Fig. 1. Post-stimulus undershoots were clearly observed in both BOLD and CBF data, not only following neuronal stimulation, but also following HC modulation, in a majority of subjects. Statistical analysis revealed no dependence of the duration or amplitude of the undershoot on HC level in either the visual or sensorimotor cortex (Table 1). In addition, there was clearly no dependence of the BOLD or CBF undershoot parameters on stimulation duration (Table 2).

Conclusion

The BOLD and CBF undershoots observed in HC responses are evidence of an origin other than $CMRO_2$ change for the BOLD post-stimulus undershoot. This argument is bolstered by the lack of correlation between undershoot magnitude or duration and stimulation duration for either BOLD or CBF. Collectively, these observations suggest that a sustained post-stimulus $CMRO_2$ increase is not likely the dominant contributor to the BOLD undershoot, and instead, support a bio-mechanical origin. Finally, the presence of consistent CBF post-stimulus undershoots suggests that the BOLD undershoot may be largely a flow-mediated response, and a hypothesis requiring further investigation.

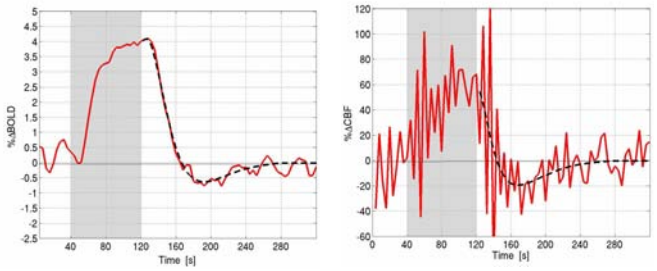

Figure 1 Unfiltered (solid red) BOLD (left) and CBF (right) time courses overlaid with the fitted undershoot (dotted black) obtained from filtered time courses for one subject using 10% hypercapnia ("on" over shaded region).

Table 1. Summary of hypercapnic perturbation results (Experiment 1).

		Amplitude [%Δ] mean±stderr		*FWHM [s] mean±stderr*	
		5% HC	10% HC	5% HC	10% HC
VC	BOLD	-0.41±-0.15	-0.18±0.12	23.71±9.88	13.99±9.63
	CBF	-14.67±5.21	-16.19±5.62	19.95±8.60	21.06±9.43
		BOLD: p = 0.27 CBF: p = 0.85		BOLD: p = 0.48 CBF: p = 0.93	
SMC	BOLD	-0.22±0.08	-0.29±0.13	19.55±8.57	23.43±9.31
	CBF	-22.04±14.17	-33.14±17.70	34.87±20.26	24.75±14.29
		BOLD: p = 0.68 CBF: p = 0.29		BOLD: p = 0.82 CBF: p = 0.78	

Table 2. Summary of stimulus duration study results (Experiment 2).

		Amplitude [%Δ] mean±stderr				*FWHM [s] mean±stderr*			
		20s on	40s on	80s on	120s on	20s on	40s on	80s on	120s on
VC	BOLD	-0.97±0.14	-0.91±0.07	-1.05±0.14	-1.11±0.13	26.71±3.96	23.64±3.31	23.03±4.07	17.79±3.71
	CBF	-18.95±2.05	-21.38±6.36	-23.99±5.22	-27.35±7.65	26.02±5.10	20.51±6.23	24.74±7.29	24.65±5.15
		BOLD: p = 0.70; CBF: p = 0.76				BOLD: p = 0.14 CBF: p = 0.95			
SMC	BOLD	-0.33±0.07	-0.39±0.10	-0.30±0.09	-0.50±0.13	16.31±3.75	8.37±4.06	4.82±4.79	15.08±5.87
	CBF	-11.83±3.43	-10.42±3.33	-12.10±4.84	-8.39±3.36	11.37±3.97	13.23±6.20	11.74±6.02	5.23±4.45
		BOLD: p = 0.24; CBF: p = 0.90				BOLD: p = 0.27 CBF: p = 0.72			

[1] Buxton *et al*. Magn Reson Med 1998;39:855-64; [2] Lu *et al. J Cereb Blood Flow Metab* 2004;24:764-70; [3] Warnking *et al.* Magn Reson Med 2004;52 :1190-9; [4] Glover GH. NeuroImage 1999;9:416-429.