# Cerebral arterial and venous blood volume changes during the post-stimulus BOLD undershoot period

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## Introduction

The BOLD signal relies on the content of deoxyhemoglobin (dHB), which mediates from changes in cerebral blood flow (CBF), blood volume (CBV) and metabolic rate of oxygen ($CMRO_2$). The post-stimulus undershoot has been often observed (1-6), however, its physiological source is still controversial. Two main ideas have been proposed. After cessation of stimulation, CBF and CBV return to the baseline quickly and a continued increase of $CMRO_2$ induces a BOLD undershoot (3,4), while a delayed compliance of CBV return induces post-stimulus undershoot (5). However, total CBV ($CBV_t$) measured by MRI contains both BOLD-insensitive arterial and BOLD-sensitive venous blood volume ($CBV_a$ and $CBV_v$), but only a sustained increase in $CBV_v$ induces the BOLD undershoot. Therefore, $CBV_v$ measurements are necessary for better understanding of BOLD undershoot source. In this study, functional $CBV_a$ and $CBV_t$ changes ($\Delta CBV_a$ and $\Delta CBV_t$) were measured in the same animals with magnetization transfer (MT)-varied fMRI (6) and contrast-agent fMRI techniques (5), respectively. Temporal characteristics of $\Delta CBV_t$, $\Delta CBV_a$, and $\Delta CBV_v$ were determined and compared with BOLD fMRI.

## Methods

Seven female adolescent cats weighing 1.0-1.5 kg were studied on a 9.4-T MRI (Varian) system using a single surface coil. Animals were maintained within normal physiological ranges under 0.9-1.1% isoflurane-anesthesia. During 40-s stimulation, binocular full-field visual stimuli were presented with square-wave high-contrast moving gratings. General imaging parameters were FOV = $2.0 \times 2.0$ $cm^2$, slice thickness = 2 mm. $\Delta CBV_a$ and $\Delta CBV_t$ fMRI was performed by GE-EPI with in-plane resolution = 312 μm x 312 μm, and flip angle ≈ 20°. Stimulus-induced $\Delta CBV_a$ measurements were performed with TR = 1 s and TE = 20 ms. Three (or two) targeted MT ratio (MTR) values (= 0, (~0.3) and ~0.6, in randomized order) in gray matter were achieved by adjusting the power level of MT-inducing RF pulses (+5 kHz off-resonance). Normalized stimulation-induced signal changes with MT were linearly fit against normalized baseline signal with MT (1-MTR), and $\Delta CBV_a$ was obtained from the intercept (6). For $\Delta CBV_t$ fMRI with TR =1s and TE = 13 ms, 7-15 mg/kg monocrystalline iron oxide nanoparticles were injected, and stimulus-induced percentage $CBV_t$ changes ($\Delta CBV_t/CBV_t$) were calculated as previously described (5). We converted $\Delta CBV_t/CBV_t$ to $\Delta CBV_t$ by estimating baseline $CBV_t$, assuming the peak amplitude of $\Delta CBV_t$ = the peak amplitude of $\Delta CBV_a$. Then, $\Delta CBV_v$ was obtained from the subtraction of $\Delta CBV_a$ from $\Delta CBV_t$.

## Results and Discussion

Post-stimulus BOLD undershoots were observed in all seven animal data (Fig. 1). Both $\Delta CBV_a$ (red) and $\Delta CBV_t$ (black) time courses showed rapid, positive changes after stimulus onset followed by small undershoots after stimulation, while $\Delta CBV_v$ (blue) slowly increased after stimulus onset, and then slowly decreased during the post-stimulus BOLD undershoot period. Fig. 2 shows normalized CBV and BOLD signals after the cessation of stimulation (80 s). Slow return of venous CBV (blue trace) contributes to the negative change of BOLD signal (green trace), which agrees with $\Delta CBV_v$ measurements in humans (7). Since ΔCBF is mediated by $\Delta CBV_a$, transient CBF decrease is expected during the post-stimulation period, which will result in a transient decrease in venous oxygen saturation level. The post-stimulus CBF undershoot was also observed previously (7,8). Our findings suggest that both post-stimulus CBF undershoot and slow $CBV_v$ return contribute to the post-stimulus BOLD undershoot. Since dynamic differences between venous and total CBV change exist, $\Delta CBV_v$ (instead of $\Delta CBV_t$) should be measured to explain the source of the BOLD signal.

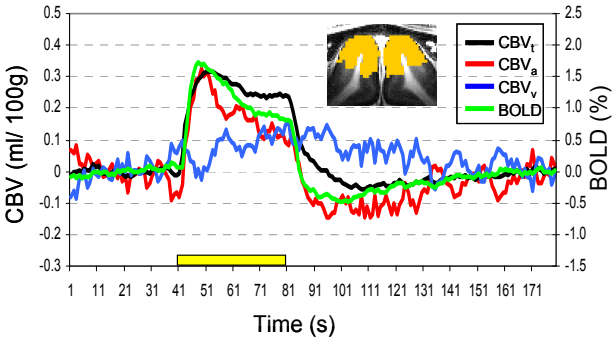


**Fig. 1.** Averaged time courses (n = 7) of $\Delta CBV_a$ (red), $\Delta CBV_t$ (black), $\Delta CBV_v$ (blue) and BOLD signal (green) were obtained from the intracortical ROI in the visual cortex (yellow pixels in inserted figure). Yellow bar: 40-s stimulation period.

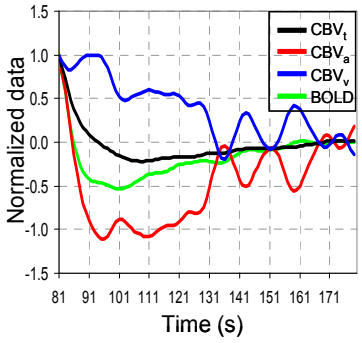


**Fig. 2.** Normalized $\Delta CBV_a$, $\Delta CBV_t$, $\Delta CBV_v$ and BOLD signal during the post-stimulus period. Cubic smoothing spline was applied.

**References 1.** Frahm et al., JMRI 2, 501-5 (1992). **2.** Ogawa et al., PNAS 87, 9868-72 (19'92). **3.** Frahm et al., MRM 35, 143-8 (19'96). **4.** Lu et al., JCBFM 24, 764-70 (2004). **5.** Mandeville et al., JCBFM 19, 679-89 (19'99). **6.** Kim et al., MRM 60, 1518–23 (2008). **7.** Chen and Pike, Neuroimage 46, 559-68 (2009). **8.** Jin and Kim, Neuroimage 43: 1-9, (2008).

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