The Coupling Between BOLD, CBF, CBV, and SEP Responses Under NO Blockade

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Introduction A detailed understanding of the mechanism linking local neuronal activity to cerebral hemodynamics is critical for interpretation of the hemodynamically weighted signals obtained via functional neuroimaging techniques. In the current work, we investigated the role of nitric oxide, a prominent vasodilator [1], in the coupling between BOLD, CBF, CBV, and neuronal responses to functional stimulation in an anesthetized rodent model.

Methods The experiment was conducted on fourteen α-chloralose anesthetized Sprague-Dawley rats. A continuous ASL sequence (2.253 s RF pulse, 2 cm proximal to isocenter; 200 ms post labeling; TR/TE 2500/25 ms; 200x200x2000 μm^3) was used to measure CBF and BOLD responses prior to and following an i.p. bolus (50 mg/kg) of 7-nitroindazole (7-NI), an *in vivo* inhibitor of the neuronal nitric oxide synthase. MION (20 mg/kg) was administered i.v. to allow CBV quantification; and somatosensory-evoked potentials (SEPs) recorded via intracranial electrodes. The functional paradigm comprised 45 epochs of 45s off/30s on/45s off blocks, with the stimulation interval made up of 90 0.3-ms, 2-mA pulses, played out at 3 Hz. The bolus of 7-NI was administered 15 mins following the commencement of the experiment and the measurement continued for another 75 mins. The MRI experiments were carried out on a 7 T (13.0 cm) Bruker BioSpec/AVANCE system (Ettlingen, Germany).

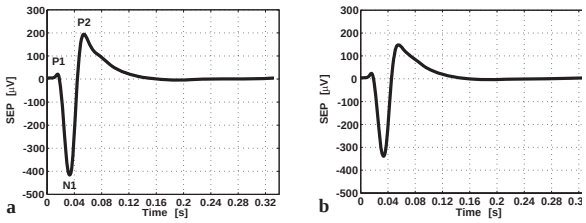

Figure 2. SEP traces in a typical subject, averaged over the epochs during predrug baseline (a), and post-7-NI bolus administration (b).

Results The average pre-drug CBF response was 48 ± 2 %; BOLD, 4.5 ± 0.1 %; and CBV (in a separate group of animals) 19 ± 3 %. The bolus of 7-NI had a significant effect ($p<10^{-6}$) on the stimulation-elicited CBF, BOLD and CBV changes in each animal, without affecting the baseline perfusion. As shown in Fig 1., the CBF response was attenuated by 89 ± 2 %, while BOLD decreased by 62 ± 1 % and CBV declined by 51 ± 3 % w.r.t. their respective magnitudes prior to treatment. The average SEP (N1-P2) amplitude decreased ($p<10^{-5}$) by only 24±7 % of its pre-drug baseline value, with no significant changes in SEP latencies (p>0.1). The SEP traces in a typical subject are shown in Fig. 2.

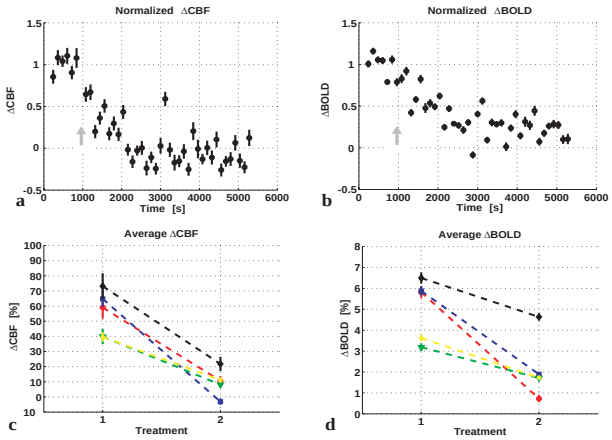

Figure 1. Epoch-to-epoch CBF (a) and BOLD (b) responses expressed in percents of the neighboring baseline, then normalized to their respective mean pre-drug baseline value (grey arrow indicates the time of 7-NI bolus). The average epoch activation-induced changes in CBF (c) and BOLD (d) signals before and after 7-NI bolus .

Discussion In agreement with the suggested role of nitric oxide in the elicitation of functional hyperemia [3,4], we observed a pronounced decrease of the hemodynamic response to functional stimulation following neuronal nitric oxide synthase inhibition. In contrast, post 7-NI neuronal responses were largely preserved. In view of the disproportionately large hemodynamic, relative to neuronal response attenuation, the data describe a prolonged, pharmacologically induced disruption in the cerebrovascular coupling and are indicative of a metabolic buffer in the tissue. The persistence of a positive BOLD response despite a near abolishment of the CBF increase and an attenuated CBV increase is in disagreement with the conventional BOLD signal models and warrants further investigation.

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