An Investigation of the VASO Contrast Mechanism Reveals a Novel Method for Quantifying Cerebral Blood Flow

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Introduction. Vascular space occupancy (VASO)-dependent fMRI is a novel imaging technique that uses the selective nulling of blood to detect cerebral blood volume (CBV) changes in regions of microvascular vasodilation and vasorestriction (1). It is shown that, at high magnetic field (3T) and high spatial resolution, the VASO effects become too large to originate from CBV effects alone. We investigated the potential sources of these VASO signal changes during visual activation as a function of MR imaging parameters (TR, TE, and SNR) and spatial resolution. The results show that multiple components contribute. Most importantly, there is an arterial spin labeling contribution to the VASO signal, which is most noticeable at short repetition time (TR). In addition, there is a large influence from partial volume contamination by cerebrospinal fluid (CSF), which will cause VASO gray matter (GM) signal changes to become more negative, most noticeably at long TR and long echo time (TE). For larger voxel sizes, partial volume contamination with white matter (WM) will reduce activation effects. When the entirety of contributions are accounted for, multi-TR VASO experiments can be designed that allow for the extraction of cerebral blood flow (CBF) and CBV within a single pulse sequence.

Methods. *Theory:* Assuming effective blood nulling, the MR signal in activated voxels can be described with a three-compartment model (Eq. 1), with water volume fractions, x_i. Signals can be described by three terms (Eq. 2), for spin density, T_1, and T_2 dependencies. C_i is water density in ml water/ml tissue; $CBV_{CSF} = 0$. The effect of arterial spin labeling due to the use of a non-selective inversion pulse in the VASO pulse sequence changes the TR-dependent magnetization term (Eq. 3) during activation, because the apparent tissue T_1 changes due to the contribution of flow (f = CBF in units of ml/g/s) in GM, as described by Eqs. 4,5 (λ=0.9 ml/g). WM has a baseline CBF contribution, while CSF has zero blood flow.

$$S_{tot} = (1 - x_{CSF} - x_{WM}) \cdot S_{GM} + x_{WM} \cdot S_{WM} + x_{CSF} \cdot S_{CSF} \quad (1) \qquad S_i \sim (C_i - CBV_i \cdot C_{blood}) \cdot M_i(TI,TR) \cdot e^{-TE/T2} \quad i = GM, WM, CSF \quad (2)$$

$$M_i(TI,TR) = M_0 \cdot [1 - (2 - e^{-(TR-TI)/T1app,i} - 2c) \cdot e^{-TI/T1app,i} - 2c \cdot e^{-TI/T1blood}] \quad (3) \qquad 1/T1_{app,i} = 1/T_{1,i} + f_i/\lambda \quad (4) \qquad c = (f_i/\lambda)\left(1/T1_{app,i} - 1/T1_{blood}\right) \quad (5)$$

Experiment: Visual simulation with yellow/blue flashing checkerboard (60s/30s off/on; 3 repetitions) was performed (n=5). VASO signal changes were measured at high spatial resolution of 1.89x1.89x3mm^3 (10.7 μl) for 6 TRs (2,3,4,5,6,7s) at TE=44 ms, 4 TEs (24,34,44,54 ms) at TR=3s, and 4 voxel volumes (10.7, 14.7, 21.1 32.9 μl) at TE = 44 ms each for short TR=2s and long TR=7s Thus, for each subject there were a total of 18 measurements. Requirement for voxel activation were cc<-0.15, SNR≥20, and cluster size > 15.

Results and Discussion. Fig. 1 shows model predictions for VASO signal changes as a function of TR (Fig. 1a), assuming a healthy CBF rest/act=65/110 ml/100g/min and CBV rest/act=0.055/0.072 ml blood/ml parenchyma. When CBF is included, the signal changes show a clear TR dependence. When accounting for the spin echo BOLD effect, the changes reduce (Figs. 1b,c), but inclusion of a CSF contribution (15%) greatly increases the VASO effect, especially at long TR and TE. Experiments show that activation is well localized to occipital GM for the visual task (Fig. 2a), and hemodynamic time courses show a large negative signal change of 6-7% at TR = 2s (Fig. 2b) and smaller negative change at TR=7s (Fig. 2c) in line with model predictions. We investigated whether CBF was quantifiable by performing a multivariate fit to the TR, TE and resolution data for baseline CBF, active CBF, active CBV and CSF/WM volume fractions assuming a known baseline CBV = 0.055 ml blood/ml parenchyma. Fig. 3 shows that fitting is achievable and gives physiologically reasonable results (CBF rest/act = 71/119 ml/100g/min; CBV act= 0.067 ml blood/ml parenchyma; $x_{CSF} = 0.18$, $x_{WM} = 0.01$). This work explains the larger-than-expected signal changes observed using VASO in terms of a large CBF and large CSF contribution, the latter even at high spatial resolution. *Importantly, it also proposes a novel non-invasive method for quantifying CBF using a simple TR-dependent experiment.*

References. 1. Lu et al. *MRM:**50**(263-274)* 2003. **2.** Lu et al. *ISMRM:**#27*** 2005. **3.** Zhou et al. *MRM:**41**(1099-1107)* 1999.

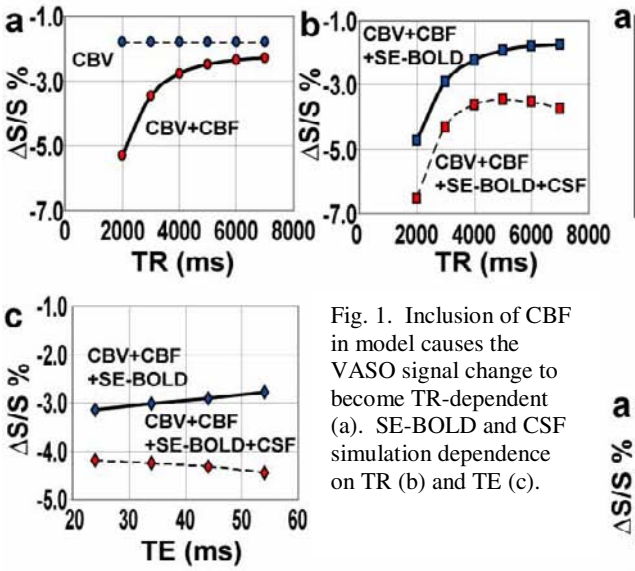

Fig. 1. Inclusion of CBF in model causes the VASO signal change to become TR-dependent (a). SE-BOLD and CSF simulation dependence on TR (b) and TE (c).

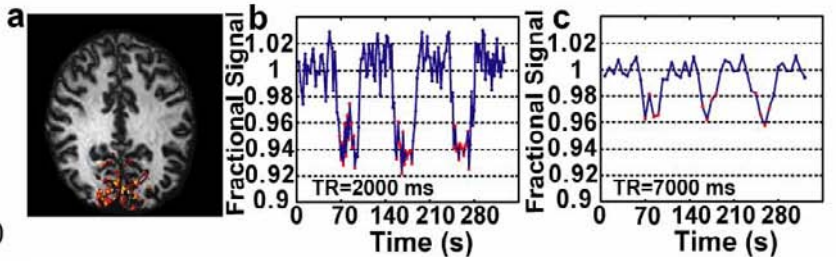

Fig 2. Activation map for TR=2s (a) and corresponding hemodynamic time course (b). When TR=7s (c), signal changes become much smaller since the arterial spin labeling effect decreases with TR.

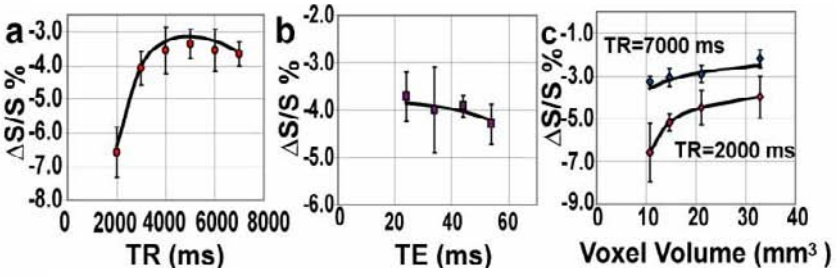

Fig. 3. Multivariate fit (solid line) results for TR (a), TE (b) and resolution (c) VASO experiments.