A theoretical and experimental investigation of vascular-space-occupancy (VASO) blood nulling times: influence of hematocrit and oxygenation on null times and CBV quantification

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Introduction. Vascular-space-occupancy (VASO) functional MRI (fMRI) is a non-invasive T_1-weighted approach for assessing CBV adjustments concurrent with neuronal activation [1-3]. Since blood water T_1 (3T: $T_{1,b}$~1550-1750 ms [4]) is longer than tissue water T_1 (3T: $T_{1,t}$~800-1300 ms [4]), following a non-selective inversion, a VASO image can be acquired at an inversion time (TI) when longitudinal blood magnetization (M_z) is zero, yet tissue M_z is positive. Assuming minimal blood water signal, vasodilatory CBV increases during elevated neuronal activity can be inferred from relative signal reductions (ΔS/S). An important concern in accurate CBV quantification pertains to the completeness of blood water nulling. Residual blood signal will not only reduce VASO sensitivity, but will lead to more negative ΔS/S [5,6]. VASO ΔS/S has been reported in the range of -1 to -6%, translating to a CBV change (ΔCBV) of 10-60%. However, high-resolution animal data suggests that ΔCBV≈10-30% [7]. Therefore, VASO ΔS/S is often too large to be attributed to CBV alone. Recently, it was shown that by using large body coils for RF transmission [5], long TR [5,6], and post-saturation pulses [8], it is possible to reduce blood signal in steady-state VASO images and obtain more physiologically plausible ΔS/S. However, a remaining concern is that $T_{1,b}$ generally used for TI calculation corresponds to average macrovascular blood water, yet CBV changes occur in microvasculature. Since $T_{1,b}$ varies with oxygenation and hematocrit (Hct) [4], it would be useful to know if VASO contrast can be improved by using a TI specific to *microvascular* $T_{1,b}$. Here, we calculate $T_{1,b}$ for varying oxygenation and Hct values corresponding to six possible vascular compartments and perform VASO fMRI experiments to demonstrate the effect of the respective blood nulling TIs.

Methods. All subjects (n=8; age=31±5) provided informed, written consent and were scanned at 3.0T (Siemens). Six visual fMRI experiments, corresponding to six different TIs, were performed on each subject. Scan parameters: gradient echo EPI, TR=5s, TE=13 ms, spatial resolution=3.5x3.5x3.5 mm^3, body coil RF transmission and 12-channel head coil reception (GRAPPA=3). We use a relatively long TR=5s to limit blood/tissue water exchange and inflow effects [5,6]. The visual paradigm consisted of 45s/30s off/on blue-yellow flashing checkerboard (f=8 Hz) x 3. TI was calculated based on $T_{1,b}$ measurements using bovine blood data from Lu et al. [4]. A linear trend of $T_{1,b}$ with Hct was demonstrated for (a)rterial (Y_a=0.92±0.07; $T_{1,a}$=[0.52·Hct+0.38]$^{-1}$) and (v)enous (Y_v=0.69±0.08; $T_{1,v}$=[0.83·Hct+0.28]$^{-1}$) blood. Here, $T_{1,b}$ and corresponding VASO TI were calculated for blood in six approximate compartments: arteries (Hct=0.42; Y_a), arterioles (Hct=0.37; Y_a), venules (Hct=0.37; Y_v), veins (Hct=0.42; Y_v), average of arterioles and venules (microvascular average), and average of arteries and veins (macrovascular average) (Table 1; left). *In vivo*, vessels will span a range of Hct; the choices above are approximations. The effect of $T_{1,b}$ variation due to reduced microvascular Hct=0.37 (macrovascular Hct=0.42) is reflected in a slight thickening of the blood recovery curve (Fig. 1a). Fig. 1b demonstrates the small range of variation in the blood signal close to respective TIs. Data were corrected for motion and baseline drift, and time courses in voxels meeting activation criteria (z<-2.5, cluster size>3, SNR>20) in all TI scans were recorded [6].

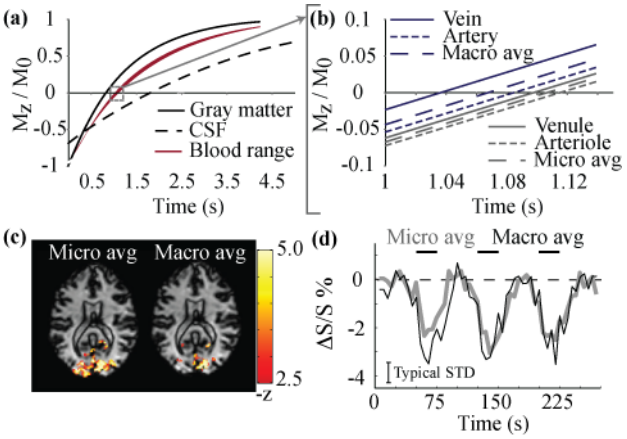

Figure 1. (a) Voxel component recovery curves. (b) Blood recovery curves close to TI. (c) Activation maps. (d) Micro and macrovascular time courses.

Results. Representative activation maps (Fig. 1c) and averaged time courses for all subjects (n=8) (Fig. 1d) are shown for TI corresponding to microvascular and macrovascular TIs. Table 1 (right columns) shows ΔS/S, calculated ΔCBV [6], number of activated voxels, and SNR for the six different TIs. Neither ΔCBV, number of activated voxels, nor SNR showed a *statistical* (P>0.05) difference between TIs. ΔS/S tended toward more negative values for shorter TIs. This trend was significant for TI corresponding to venous (P=0.036) and average macrovascular (P=0.043) blood compared to microvascular blood.

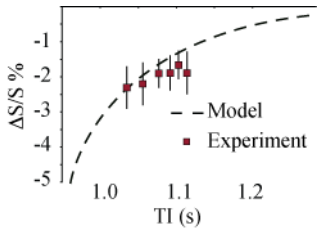

Figure 2. VASO model comparison (Piechnik et al. [9]) with experimental data.

Discussion. VASO ΔS/S is reproducibly similar (ΔS/S = -1.7 to -2.3 %; ΔCBV = 18.9 to 22.9%) over a TI range corresponding to Hct=0.37-0.42 and *Y*=69%-92%. Thus, fresh blood contributions from non-nulled blood, which have been reported in the literature [5,8] and minimized here (TR=5s), outweigh variations due to Hct or oxygenation differences over this range. The weak dependence of VASO ΔS/S on TI agrees in principle with the previously reported model of Piechnik et al. [9], shown by the dashed line in Fig. 2. This model utilized 19 blood compartments with reactivity distribution based on data from CO_2 challenges [9,10]. The simulation was performed with voxel volume fractions CSF / gray matter / white matter / blood = 10% / 70% / 2% / 8%. ΔCO_2 = 20 mmHg induced vasodilatation was assumed, resulting in a CBF and CBV change of approximately 100% and 30%, respectively. The choice of the simulation parameters corresponds roughly to an archetypal reactive voxel postulated in VASO simulations [1,6]. In contrast to postulated large differences in $T_{1,b}$ in specific vascular compartments [9,10], the examined range of VASO TI for microvascular vs. macrovascular blood $T_{1,b}$ represents the averaged blood pools and is relatively small. Independently of blood signal, imaging at longer TI decreases the residual CSF $|M_z/M_0|$ for voxels at the CSF/tissue border, whereas residual tissue $|M_z/M_0|$ increases. The interaction between these mechanisms may be responsible for the departure of the measurements from prediction for longer TIs as only voxels with negative *z*-scores were analyzed here. High spatial resolution studies with shorter TR/TI where VASO ΔS/S is more sensitive to choice of TI (Fig. 2) and a different analysis incorporating all voxels may prove useful for understanding additional mechanisms of VASO contrast and is the focus of ongoing work.

Conclusion. At the spatial resolution where VASO is frequently performed and at long TR/TI, nulling microvascular vs. macrovascular blood water is not an overwhelming complication in ΔCBV estimation. In agreement with previous reports [6,9], we show that the choice of TI predictably influences the observed sensitivity of VASO to functional stimulation but that this influence is small at long TR over a $T_{1,b}$ range corresponding to typical variation in average blood oxygen saturation and hematocrit. Work with a wider range of TI and at high-spatial resolution should help to further unravel the details of VASO contrast.

Table 1

	Blood Nulling		*Experimental (n=8)*			
	T_1 (ms)	TI (ms)	ΔS/S %	ΔCBV %	# Voxels	SNR
Arteriole	1747	1114	-1.9±0.6	21.6±3.3	134±28	35±4
Venule	1703	1092	-1.9±0.4	20.7±2.2	132±21	36±6
Micro Avg	1725	1103	-1.7±0.5	18.9±2.7	143±30	37±7
Artery	1671	1077	-1.9±0.4	20.3±2.1	139±22	34±5
Vein	1591	1035	-2.3±0.6	22.9±3.0	130±16	28±3
Macro Avg	1631	1056	-2.2±0.6	23.2±3.1	152±29	34±5

References. [1]Lu et al. MRM. 2003; 50. [2]Jin et al. Neuroimage. 2008;40. [3]Ho et al. Neuroimage. 2008;41. [4]Lu et al. MRM 2004;52. [5]Donahue et al. ISMRM. 2008;#2391. [6]Donahue et al. MRM 2006;56. [7]Hillman et al. Neuroimage. 2007;35. [8]Lu H. ISMRM. 2008;#406. [9]Piechnik et al. ISMRM. 2006;#1541. [10]Piechnik et al. Neuroimage.2008;39. **Funding.** The Oxford NIHR Biomedical Research Centre and Dunhill Medical Trust.