Hemodynamic characteristics in various arteriolar segments upon physiological changes

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INTRODUCTION: It is interesting to characterize the spatial and temporal behavior of microvascular flow changes upon physiological alterations, particularly because functional imaging depends on the tight relationship between local hemodynamics and neuronal activity. Studies of hemodynamic regulation on a fine scale has typically been done in animals using contrast agents and invasive techniques [1-4]. Our study investigated human neurovascular responses to graded visual stimulation and hypercapnia, while targeting varying sections of the microvascular tree. Using a recently developed non-invasive, arterial spin labeling method – QUASAR [5], we derived model-free estimations of CBF and arterial blood volume (aBV), and detected changes in arterial and microvascular arrival times for various stimulation intensity and end tidal CO_2 levels. Furthermore, varying the crusher gradients allowed us to target different arteriolar segments.

METHODS: ***Experiments:*** Six healthy subjects (2M, 2F; 26-33 yrs) were presented with graded visual stimuli with and without hypercapnia and scanned using QUASAR [5] sequences with different crusher encoding velocities (Venc) on a Philips Intera 3.0T imager. Informed consent was obtained. The functional paradigm was a gray-white, 8Hz flashing checkerboard pattern (25% and 100% contrast) that alternated with an iso-luminance 50% gray baseline condition. There were 4 runs per subject using: (1) No crusher gradients and (2-4) Venc=3/6/9 cm/s. Each run consisted of 2 sub-runs (5 blocks 'off' (15 vols each), 4 'on' (10 vols each)) with a baseline period in between the 2 sub-runs. Subjects breathed medical air using non-rebreathing circuitry during the first sub-run and were switched to a gas mixture of 8% CO_2, 21% O_2, balance N_2 after the second activation period. End tidal pCO_2, Ysat, pulse, and respiratory rate were monitored using MR-compatible InVivo monitoring system. ***MR parameters:*** QUASAR: Venc=[∞, 3/6/9 cm/s], TR/TE_1/TE_2=3000/21/37 ms, ΔTI=200 ms, time points=14, α=35°, SENSE factor=3, labeling slab=150 mm, inversion gap=20 mm, slices=3, thickness=5 mm, gap=1 mm. Slices were aligned with the calcarine sulcus to image the primary visual cortex. ***Data Analysis:*** A 7mm Gaussian filter was applied prior to statistical analysis. Linear interpolation was done before pair-wise subtraction to avoid BOLD effects [6]. Tissue curves, ΔM(t) for each condition were derived voxel-by-voxel from the crushed and non-crushed data. RS-tests ($p<0.001$, uncorrected) were performed to determine the activated regions. Only commonly activated voxels for each subject were selected for further analysis. To quantify CBF changes during activation and to derive the various arrival times, we used [6]: $\Delta M = 2 \bullet M_{a,0} \bullet f \bullet \int_0^t c(\tau) \bullet r(t-\tau) \bullet m(t-\tau) \bullet d\tau$; [$M_{a,0}$ – arterial blood equilibrium magnetization; f – flow; c(t) – AIF; r(t-τ) – residue function; m(t-τ) – longitudinal magnetization relaxation]. Data from the first 75s after the start of the CO_2 condition, including the first 5 volumes of each baseline block and the first 3 volumes of each visual block were excluded to ensure steady state measurements. Perfusion curves were averaged across volumes in identical conditions to increase SNR. Arterial Input Functions [$AIF(t) = 2 \bullet M_{a,0} \bullet c(t)$] were estimated by subtraction of crushed from non-crushed tissue curves [5]. τ_a and τ_m were estimated by detecting rising edges on AIFs and crushed tissue curves respectively. Absolute AIFs and aBV were estimated according to the method in [5]. ANOVAs were performed to assess statistical significance of the measured variables by condition.

RESULTS: Task-related increases in CBF were seen in both normocapnia and hypercapnia (end tidal pCO_2 ranged 49-65mmHg). 'Tissue' perfusion curves appeared to enlarge with decreasing crusher strength, reflecting the fact that a larger portion arteriolar vessels were included in these measurements, while the fractional AIFs shrunk (Fig 1). The normally smooth 'tissue' curves also narrowed at the peaks and shifted forward in time, becoming more AIF-like. Such effects were increased under hypercapnia due to vasodilation and increased flow. Table 1 describes CBF, aBV and arrival time values. CBF increased with visual contrast ($F=4.1$, $p=0.02$) and hypercapnia ($F=7.6$, $p=0.01$), but varying crushing gradients did not seem to affect CBF ($p>0.05$). The aBV increased with hypercapnia ($F=5.2$, $p=0.03$), but did not reach significance for visual contrasts and crushing levels. Both arterial (T_a) and microvascular (T_m) arrival times shortened significantly with lower crusher levels ($F=3.4/7.6$, $p=0.04/0.001$) (Fig 2). Additionally, T_m significantly shortened with visual stimulation ($F=5.3$, $p=0.03$). T_a and T_m appeared slightly shorter in hypercapnia, but did not reach significance.

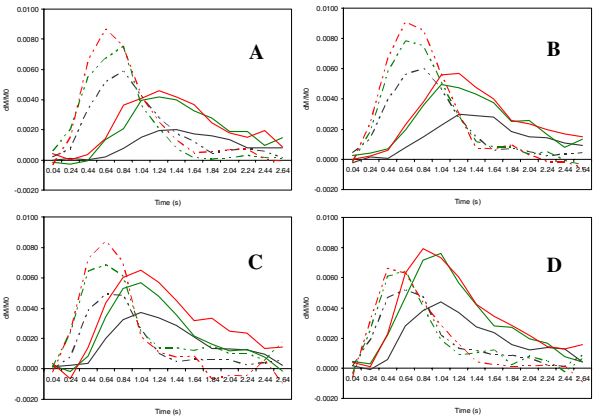

Figure 1: Tissue curves (solid lines) and fractional AIFs (broken lines) for visual contrast / baseline conditions (red: 100% VC, green: 25% VC, gray: baseline). (A) Air with Venc 3cm/s. (B) CO_2 with Venc 3cm/s. (C) Air with Venc 9cm/s. (D) CO_2 with Venc 9cm/s. Note the significant change in shapes and amplitudes, especially between (A) and (D).

DISCUSSION: Our results illustrate the interactions of capnic levels on various arteriolar compartments during task-related hemodynamic responses on a fine scale. Consistent with literature, CBF and T_m increase significantly with task/neuronal activity, while CBF and aBV show positive reactivity with hypercapnia. Targeting different segments of the arteriolar tree through varying crusher gradients significantly modulated the arrival times. From Fig 2, the distinctly shorter T_a and T_m in the Venc 9cm/s condition could possibly suggest a certain transition on the vascular level. With capillary flow at below 1cm/s even in hypercapnia [3,7], the strongest crusher level of Venc 3cm/s would leave the capillaries untouched. It is likely that certain flow along small to mid-sized arterioles was crushed at Venc=3cm/s, however stronger crusher gradients targeting even smaller vessels would result in a rapid decrease in SNR. Recent studies have shown the importance of the microvasculature in influencing delivery of oxygenated blood during increased neuronal activity, through myogenic and pericytic controls around the arterioles, capillaries and their junctions [4,8]. QUASAR offers a non-invasive way to probe hemodynamic changes for different arteriolar segments and under various neurovascular challenges. Preliminary conclusions from this study appear to indicate that most of the resistance changes upon stimulation happen past arteriolar segments in which blood velocity is below 9 cm/s.

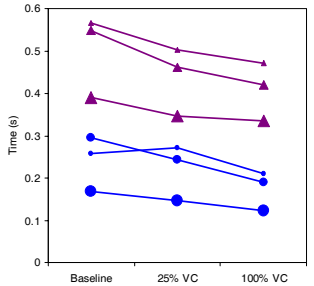

Figure 2: T_a (blue lines) and T_m (purple lines) across increasing levels of visual stimulation and crusher gradients (Venc 3/6/9 cm/s: smallest/medium/largest nodes respectively). Note the much reduced times for Venc=9cm/s values vs. the others.

REFERENCES: [1] Cox et al (1993) JCBFM 13:899-913; [2] Malonek et al (2005) Science 272:551-54; [3] Hutchinson et al (2006) NI 32:520-30; [4] Peppiatt et al (2006) Nature 443:700-4; [5] Petersen et al (2006) MRM 55 :219-32; [6] Buxton et al (1998) MRM 40:383-396; [7] Villringer et al (1994) Circ.Res. 75 :55-62; [8] Harrison et al (2002) Cereb.Cortex 12 :225-233.

Table 1: CBF, aBV, T_a and T_m (means and standard errors) for baseline vs. visual stimulation (contrast conditions averaged) and air vs. CO_2. Values here are collapsed across crusher levels for simplicity. CBF standard errors are relatively large since absolute values vary across subjects. '^' means statistical significance ($p<0.05$) for visual stimulation; '*' means likewise for CO_2.

	CBF (ml/100g/min) ^*		aBV (% of voxel) *		Ta (s)		Tm (s) ^	
	Air	CO_2	Air	CO_2	Air	CO_2	Air	CO_2
Baseline	66.9 (12.7)	146.8 (48.3)	0.563 (0.08)	0.790 (0.22)	0.246 (0.05)	0.234 (0.06)	0.530 (0.07)	0.473 (0.05)
Visual Stimulation	126.9 (25.3)	178.2 (43.9)	0.694 (0.12)	0.824 (0.16)	0.200 (0.05)	0.195 (0.06)	0.444 (0.05)	0.401 (0.05)

ACKNOWLEDGEMENT: SMF; NMRC 04/004.