Changes in arterial arrival time (AAT) and cerebral blood flow (CBF) with hypercarbia and hypercarbic hyperoxia

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Target Audience: Researchers who employ hypercarbic or hyperoxic gas challenges for ASL, calibrated BOLD, and/or cerebrovascular reactivity studies.

Purpose: Hypercarbic gas challenges are being used with increasing frequency in cerebrovascular reactivity (CVR) and calibrated BOLD applications. In both applications, independent measures of cerebral blood flow (CBF) are often required to improve interpretability of hemodynamically non-specific BOLD contrast, and as such arterial spin labeling (ASL) measurements of CBF are frequently performed, especially in research settings where invasive CBF measurements are impractical or undesirable. A common assumption in such measurements is that arterial arrival time (AAT), or the time required for blood water to reach the capillary exchange site, does not vary considerably between room air (i.e., normocarbic normoxia) and hypercarbia (i.e., either hypercarbic normoxia or hypercarbic hyperoxia) breathing. However, during neuronal activity, and in response to pharmacological manipulation of CBF using remifentanil, it has been shown that the fractional AAT reduction is approximately can be as large as the fractional CBF increase[1-3], and therefore it is likely that similar changes in AAT may occur during hypercarbic vascular stimulation. Quantifying this effect is of great importance to ASL measurements of CBF, as ASL experiments performed at a single post-labeling inversion time (TI) may bias the true CBF depending on the change in AAT. Here, we perform multi-TI ASL measurements to simultaneously quantify CBF and AAT in multiple brain regions in response to different types of common gas stimuli.

Methods: All volunteers (n=7; age=29+/-5 yrs; 4M/3F) provided informed, written consent and were scanned at 3.0T (Philips) using quadrature body coil transmit and 32-channel SENSE reception. *MRI parameters*. Pseudo-continuous arterial spin labeling (pCASL) was performed with the following parameters: spatial resolution = 4 x 4 x 7 mm^3, echo time (TE) = 11 ms, repetition time (TR) = 3.6s, averages = 13. Seven TIs were acquired in a pseudo-random order: 100 ms, 400 ms, 700 ms, 1000 ms, 1300 ms, 1600 ms, 1900 ms. Six averages per TI were obtained, which resulted in a scan duration of 302.4s. The labeling pulsetrain (duration = 1000 ms) consisted of 0.5 ms Hanning pulses. The 1000 ms duration, which is slightly shorter than the typical pCASL pulse train of 1500-2000 ms, was chosen to increase sensitivity to AAT variability. *Hypercarbic stimuli*. Multi-TI pCASL was repeated twice in each subject for three different scenarios: (i) room air (21% O_2 / 79% N_2), (ii) hypercarbic normoxia (CO2/air: 5% CO_2 / 21% O_2 / 74% N_2), and (ii) hypercarbic hyperoxia (carbogen: 5% CO_2 / 95% O_2) administration. Recordings of heart rate, respiratory rate, arterial oxygen saturation fraction (Y_a), and $EtCO_2$ were made throughout the experiment. *Analysis*. ASL images were corrected for motion, pair-wise subtracted, and averaged for each TI. Next, a single-compartment kinetic model[4] was applied, separately for each gas stimulus, and AAT and CBF were recorded (two measurements per gas type for each subject). A reduction in blood water T_1 from 1.6 to 1.4s was included in the model applied to carbogen data to correct for the hyperoxic effect on blood water T_1. AAT and CBF maps were recorded in the following regions: cerebellum, occipital lobe, frontal lobe, and parietal lobe.

Results and Discussion: **Fig. 1** shows representative slices for quantified CBF (**A**) and AAT (**B**) maps for a single volunteer, along with (**C**) multi-TI data and fitted kinetic curves for the same volunteer. CBF increases and AAT reduces cortically (P<0.05) in the CO2/air and carbogen condition relative to room air. The extent of these changes varies with region considered (n=7; **Fig. 1D** and **Table 1**). In all major brain lobes considered, relative to room air, CBF was statistically higher with both the CO2/air (P<0.05; range=14.9-24.5%) and carbogen (range=9.3-21.6%) stimulus, and AAT significantly lower (P<0.05; CO_2/air range=-13.4 - -20.6%; carbogen range=-9.2 - -12.1%). The CBF increase and AAT reduction during CO2/air was significantly larger than for carbogen (P<0.05). This provides evidence for a small vasoconstrictive effect from the hyperoxia on the CBF response to carbogen, which interestingly also may result in a significantly smaller AAT reduction (e.g., **Fig. 1B,D**). pCASL is becoming increasingly preferred over pulsed ASL owing to its increased SNR and reduced transit time sensitivity. However, pCASL labeling efficiency is also sensitive to blood water velocity, as shown in **Eq. 1**, as the phase accrual (ϕ) over the pulse train depends on the z-slice gradient (G), label position (z), gyromagnetic ratio (γ), and blood water velocity (v), relative to the inter-pulse gap (t_2-t_1). Therefore knowledge of how blood water velocity changes during periods of vascular stimulation is crucial to quantitative interpretation of CBF-weighted reactivity measurements made with pCASL. These values can be used as an exemplar for understanding to what extent ASL-measured CBF changes are influenced by changes in blood water arrival time.

Table 1	Room Air 21% O2 / 79% N2		CO2/Air 5% CO2 / 21% O2 / 74% N2		Carbogen 5% CO2 / 95% O2	
	AAT (ms)	*CBF (ml/100g/min)*	*AAT (ms)*	*CBF (ml/100g/min)*	*AAT (ms)*	*CBF (ml/100g/min)*
Parietal	713±147	56.7±8.9	566±189	65.2±14.2	647±199	62.0±14.3
Occipital	743±137	62.3±10.9	643±147	73.1±15.1	667±160	69.3±17.4
Frontal	544±68	53.6±11.2	436±121	63.4±16.9	478±89	58.7±17.2
Cerebellum	951±78	54.8±11.4	821±114	68.2±17.9	853±108	66.6±24.3
Mean±STD	**605±330**	**60.8±9.4**	**501±293**	**70.2±7.2**	**546±290**	**66.3±6.3**

$$\varphi = \gamma \int_{t1}^{t2} Gz dt = \int_{t1}^{t2} G(z + vt) dt \quad [1]$$

Conclusion: We performed serial measurements of CBF and AAT in healthy volunteers during different hypercarbic and hyperoxic gas stimuli. Results demonstrate that in addition to the well-known effect of CBF increasing with hypercarbia, AAT also reduces with hypercarbia in a regionally-specific manner.

References: **1**. Gonzalez-At JB, et al. MRM. 2000;43(5):739-46. **2**. Hendrikse J, et al. MRM. 2003;50(2):429-33. 3. MacIntosh BJ, et al. *JCBFM*. 2008;28:1514-22. **3.** Buxton RB, et al. MRM. 1998;40(3):383-96.

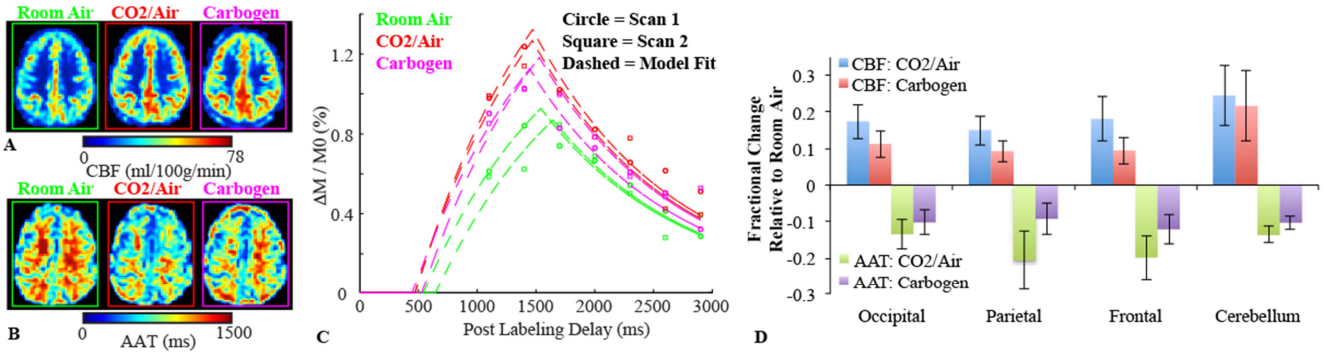

Fig. 1. *Representative volunteer slices showing (**A**) an increase in CBF and (**B**) reduction in AAT with hypercarbia relative to room air. (**C**) Multi-TI data from the same volunteer showing clear differences in AAT and CBF for the different stimuli. Results from all volunteers (n=7) are presented in (**D**) and **Table 1**.*