In vivo quantification of blood water R_1 change during hypercarbic hyperoxia

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Target Audience: Researchers utilizing blood oxygenation level-dependent (BOLD) or arterial spin labeling (ASL) magnetic resonance imaging for quantitative cerebrovascular reactivity (CVR) assessment.

Purpose: *The purpose of this study is to quantify the change in blood water R_1 that results from hypercarbic hyperoxia (i.e., carbogen) administration in vivo in humans.* Carbogen has been used in cerebrovascular reactivity (CVR) MRI studies of tumors[1] and cerebrovascular disease[2], as well as in calibrated BOLD studies[3]. Clinically, from a safety standpoint, carbogen may be preferred to hypercarbic normoxia (i.e., 5%CO_2/21%O_2/74%N_2) stimuli owing to its ability to increase the fraction of inspired O_2 (FiO_2), which enables its use as a stimulus in acute or subacute stages of cerebrovascular disease. However, from an MR perspective, the BOLD and CBF-weighted ASL signals evoked by carbogen are complex, with contributions from increases in oxygen saturation and blood water R_1, and small-to-negligible vasoconstrictive influences from hyperoxia[4]. Importantly, calibrated BOLD, or multi-modal assessments of CVR and CBF together using BOLD and ASL require a quantitative understanding of how blood water R_1 changes with carbogen administration, yet these values have only been estimated to date. Importantly, as FiO_2 increases with carbogen in a manner that is not straightforward to control *ex vivo*, blood water R_1 changes really must be measured *in vivo*. Here, we apply careful hypercarbic normoxia (5% CO_2/21%O_2/74%N_2) and hypercarbic hyperoxia (5% CO_2 / 95% O_2) stimuli sequentially in healthy volunteers in conjunction with ASL MRI. The hypothesis to be investigated is that owing to the small-to-negligible effect of hyperoxia on CBF[4], it is possible to fit for the blood water R_1 change during carbogen administration under the assumption that the identical hypercarbic fraction (i.e., 5% CO_2) is the predominant contributor to CBF changes in both stimuli types, and thus CBF changes should be similar between these two stimuli after controlling for R_1 changes. The validity of this assumption is evaluated by comparing regional variation between the CO_2 in air and carbogen-derived CBF maps.

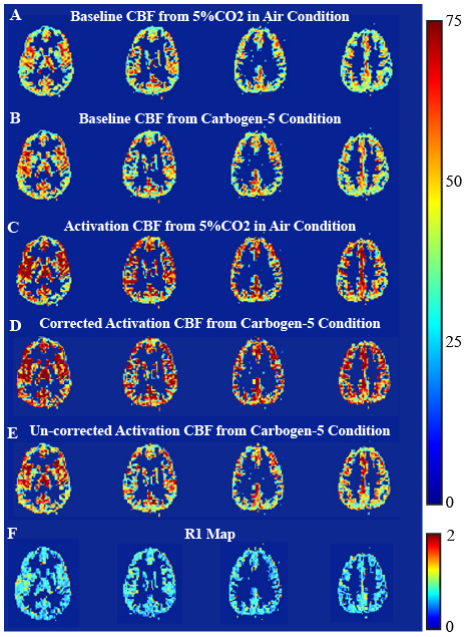

Fig. 1. Example slices of one participant in rows showing CBF (mL blood/100g of tissue/min) after thresholding for each condition: (A) baseline 5% CO_2 in air, (B) baseline carbogen-5, (C) activation 5% CO_2 in air, (D) corrected activation carbogen-5 with the calculated blood R_1 = 0.73 s^{-1}, and (E) un-corrected activation carbogen-5 with blood R_1 = 0.62 s^{-1}. (F) Map of blood R_1 values across thresholded area (s^{-1}) show limited contrast, consistent with a single value providing a correction factor for the two scans.

Methods: Healthy volunteers (n=8; 4M/4F; age=33.8±8.7yrs) provided informed, written consent and were scanned on a 3T Philips Achieva system using body coil transmit and 8-channel SENSE head coil reception. *Paradigm.* Participants were fitted with a non-rebreathing mask, and gas was delivered at 12L/min during a breathing protocol of 272.5s baseline=room air and 272.5s gas (either 5% CO_2 in air or carbogen-5). Measurements of heart rate, respiratory rate, and end-tidal CO_2 were recorded throughout the experiment. *MRI.* CBF changes were assessed using pseudo-continuous ASL (pCASL) with a single-shot EPI readout (TR=3900ms, TE=13ms, TI=1525ms; spatial resolution =3.5x3.5x7mm^3 with a inter-slice gap of 0.5mm; slices=17). Spin labeling was performed using a 1.5s string of 0.5 ms Hanning pulses. *Analysis.* Data were corrected for baseline drift and motion. CBF in both baseline conditions and both stimulus epochs (i.e., CO_2/room air and carbogen) was quantified by applying the solution to the flow-modified Bloch equation, accounting for labeling duration and magnetization transfer effects. CBF in the CO_2 in air and carbogen conditions was first quantified assuming an unchanging blood water R_1 (blood water R_1=0.62s^{-1}; assuming Hct=0.37). Next, the CBF values were filtered by applying a CBF threshold (mL/100g/min) = 20, which was used to remove fitting bias to white matter CBF which has a transit time 2-3 times longer than gray matter and could not be accurately sampled over the TI range. Finally, the blood water R_1 value during carbogen was calculated by requiring that the voxel-wise CO_2 in air and carbogen CBF change be identical.

Results and Discussion: Cortical CBF values for the two baseline conditions did not significantly differ (CO_2/air=41.1±2.8 mL/100g/min; carbogen=41.4±2.2 mL/100g/min; p=0.8), providing evidence for the pCASL method being stable in time. The average R_1 value calculated in the carbogen condition was 0.73s^{-1} ± 0.07s^{-1} (T_1=1.37s). The average standard deviation within each participant was ± 0.237s^{-1}, suggesting more variability within participants than across participants. Representative corrected and un-corrected CBF maps are shown in Fig. 1. The corrected CBF values for the activation condition with carbogen did not significantly differ from the CBF values for the activation condition with 5% CO_2 in air (CO_2/air=45.4±6.8 mL/100g/min; corrected carbogen=46.6±5.9 mL/100g/min; p=0.6), but did significantly differ from the CBF values of the un-corrected carbogen activation condition (corrected=46.6±5.9 mL/100g/min; un-corrected=38.1±4.6 mL/100g/min; p<0.01). A confounding factor could be the interplay of hypercarbia and hyperoxia (vasodilation vs. vasoconstriction) and resulting influence on CBF, as we assume here that hyperoxia has a negligible effect on CBF relative to hypercarbia. Independent ^{15}O PET work in humans has revealed a non-significant change in CBF with hyperoxia (100% O_2) in healthy volunteers, but approximately a 3 mL/100g/min reduction in CBF in chronic ischemia[4]. Therefore, the blood water R1 calculated here may be slightly overestimated (R1 range = 0.71-0.73s^{-1}; T1 range = 1.37-1.41s).

Conclusion: Carbogen-5 results in a blood water R_1 of approximately 0.73s^{-1} ± 0.07s^{-1} (T_1=1.370s) in humans, relative to a baseline R_1 of 0.63s^{-1} (T_1=1.6s). While this value can be adjusted for slight vasoconstrictive effects of hyperoxia, this value is in line with recently estimated carbogen R_1 values and should provide a valuable reference for future calibrated BOLD CVR experiments.

	5% CO_2 in Air *(mL blood /100g tissue/min)*		Carbogen-5 *(mL blood/100g tissue/min)*		
	Baseline	Activation	Baseline	Corrected Activation	Un-corrected Activation
CBF (mL/100g/min)	41.1±2.8	45.4±6.8	41.4±2.2	46.6±5.9	38.1±4.6
R_1 (s^{-1})	0.62	0.62	0.62	0.73±0.07	0.62

References: [1]Taylor NJ, *et al.* J Magn Reson Imaging 2001 Aug;14(2):156-63. [2]Zaharchuk G, *et al.* Stroke 1999 Oct;30(10):2197-204 [3]Bulte DP, *et al.* Magn Reson Med 2009 Feb;61(2):391-8. [4]Ashkanian M, *et al.* Brain Res 2009 Dec 22;1304:90-5.