The effect of graded hypercapnia on arterial cerebral blood volume (aCBV)-weighted inflow vascular-space occupancy (iVASO) contrast

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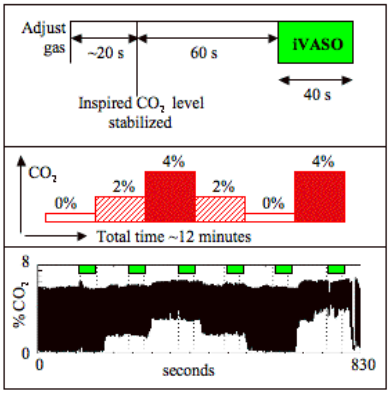
Introduction. Active cerebral blood volume (CBV) changes, facilitated by relaxation of smooth muscle surrounding arterioles, are closely related to cerebral blood flow (CBF) regulation and are incompletely understood in many cerebrovascular disorders. Furthermore, knowledge of arterial CBV (aCBV) in traditional cerebrovascular response (CVR) studies may help disentangle the many factors that operate in tandem during the vascular response to hyper- and hypocapnia. Novel MRI approaches sensitive to CBV [1], and more specifically arteriolar CBV (aCBV) [2-4] have recently emerged. One popular approach for non-invasively measuring CBV reactivity is with vascular-space-occupancy (VASO) MRI [1], which aims to null the blood water signal by acquiring an image, following RF inversion, at the precise time when longitudinal blood water magnetization is zero. The resulting data contains signal from extravascular tissue, and while changes in this signal can be used to infer changes in CBV, a significant limitation of VASO implemented in this manner is that only relative CBV changes can be detected. Recently, an improvement to the VASO technique was proposed in which the blood-nulled VASO image was interleaved with a "control" image in which blood water magnetization was nonzero, yet tissue signal was identical as in the control acquisition [5,6]. By subtracting the VASO image from the control image, a CBV-weighted map is obtained. Furthermore, by inverting only inflowing blood water as has been proposed with inflow VASO (iVASO) [4], the CBV-weighted map can be sensitized to aCBV. While the iVASO [4] and iVASO with dynamic subtraction [5,6] approaches have been proposed and preliminarily tested, much work remains on validating and completely understanding the contrast mechanism. Here, we measure the relationship between iVASO contrast and graded levels of hypercapnia in human visual cortex. The results provide information regarding the nature of the iVASO contrast mechanism, in terms of aCBV and transit time changes, and outlines the potential utility of the technique in CVR studies.

Methods. *Arterial Cerebral Blood (aCBV)-Weighted MRI.* By comparing a control image with an image where inflowing longitudinal blood water magnetization is nulled, iVASO can be used to generate aCBV-weighted maps [5,6]. Blood nulling can be achieved for a range of inversion times (TI=350-1200ms) in a steady-state iVASO experiment by adjusting the TR. Importantly, this range of TIs approximately coincides with the range of commonly reported arterial transit times [7]. Consequently, the CBV-weighting in iVASO is primarily pre-capillary, including the arterioles that are believed to be actively involved in the CBV response to hypercapnia. *Data acquisition.* Healthy volunteers (n=6; 2/4 Male/Female; age=23-26 yrs) were scanned at 3.0T (Siemens, Ehrlangen, Germany) using body coil RF transmit and 12-channel head coil RF receive. An iVASO image (TR/TE/TI=1778/18/989ms, spatial resolution = 3.5x3.5x4.0 mm^3) was centered on the calcarine fissure and aCBV-weighted maps were calculated. Subjects were fitted with a non-rebreathing face mask covering their nose and mouth which extracted all inhaled gas from a reservoir bag while directing exhalations into the room environment. Gas mixtures of 0%, 2%, or 4% CO_2 in humidified air were delivered to the reservoir at a rate of 30 liters/min. A nasal cannula was inserted underneath the mask to allow continuous sampling of the inspired and expired O_2 and CO_2 content (BIOPAC M150). Respiratory bellows were used to record breathing rate and depth. All physiological recordings were temporally aligned with the scanner trigger output. Six blocks of graded hypercapnia (two of each gas mixture) were delivered to the subject in an order designed to minimize the size of the step-changes. After changing the gas content being delivered to the reservoir, approximately twenty seconds was needed to see the subject's inspired CO_2 fraction stabilize at the desired level. The effects of the new gas mixture on the subject's end-tidal CO_2 required additional time to respond and stabilize, and thus sixty seconds was allowed for this process prior to commencement of the 40s iVASO scan. Fig. 1 shows a schematic of the gas delivery protocol.

Figure 1. Schematic of gas delivery



Analysis. For each subject, the six iVASO datasets were co-registered and corrected for motion artifacts using FLIRT [8]. A white matter ROI was used to calculate the M_0 calibration values, and ΔS="control"-"nulled"/M_0 maps were created for each subject. A second ROI was manually drawn in the visual cortex, and the mean $\Delta S/M_0$ in this region was calculated for each of the six datasets. The end-tidal values were automatically extracted from the CO_2 trace using IDL and averaged during each of the six scan periods.

Results. The CO_2 data for one subject is illustrated in Figure 1, where the end-tidal values are reflected by the upper envelope of this trace and the inspired fraction is represented by the lower envelope. These data clearly exhibit the gas delivery protocol: the large, stepwise manipulations in inhaled gas content are associated with more subtle and slower responses in the expired values. The mean end-tidal CO_2 changes observed in 2% and 4% relative to 0% CO_2 inhalation were 2.61±1.03 and 5.46 ± 1.38 mmHg, respectively. Figure 2 shows the relationship of the mean $\Delta S/M_0$ iVASO values and the graded hypercapnia for all subjects, and the correlation values and linear fit slope values are given in Table 1. A linear trend between the aCBV-weighted iVASO contrast and $etCO_2$ is observed.

Discussion. In all but one subject, a robust positive correlation was observed between the iVASO measurement and end-tidal CO_2. The iVASO contrast is dependent on both the capillary arrival time (τ; time for inverted blood water to reach capillary exchange site) and the aCBV, both of which may change during neuronal or vascular stimulation. Specifically, iVASO $\Delta S/M_0 \sim (TI/\tau)*aCBV$ [5,6]. Thus, an increase in iVASO contrast could be due to both a reduction in τ as well as an increase in aCBV, both of which may occur in conditions of increased hypercapnia. Additional experiments which separately measure transit time effects are necessary to fully understand this phenomenon. Cerebrovascular reactivity (CVR), the response of cerebral blood vessels to vasoactive agents, is of interest in understanding mechanisms of hemodynamic compromise. Techniques involving manipulations of arterial blood gas tensions in conjunction with noninvasive MRI techniques have demonstrated robust measurement of CVR in healthy subjects and populations of patients with carotid artery disease [9]. However, the methods currently dominating this field of research are primarily BOLD fMRI and to a lesser degree CBF-weighted arterial spin labeling. It is desirable to more fully assess the different vascular properties comprising the CVR response before robust clinical studies can be implemented. The iVASO metric is weighted towards pre-capillary vessels, including arterioles, which modify their resistance via changes in vascular tone in response to external stimuli and therefore may be of use in CVR investigations. In conclusion, we measured the effect of graded hypercapnia on aCBV-weighted iVASO contrast and found a strong positive linear trend between iVASO contrast and $etCO_2$ which can be explained by an aCBV increase or an equivalent capillary transit time decrease.

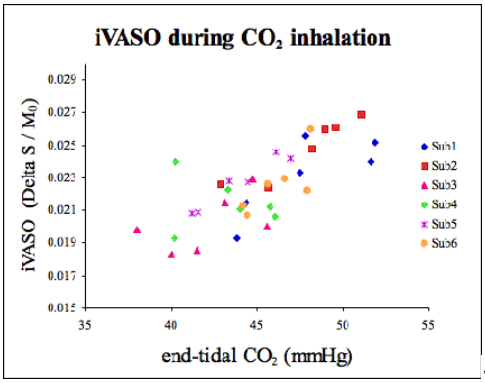


Fig 2. iVASO $\Delta S/M_0$ within ROI during hypercapnia

Subj.	1	2	3	4	5	6
R^2	.63	.88	.32	.04	.94	.57
Slope	.0006	.0006	.0003	-.0001	.0007	.0008

Table 1. Correlation (R^2) and fitted slope ($\Delta S/M_0$ / $\Delta etCO_2$ mmHg) values for six subjects.

References. [1] Lu H, et al. MRM 2003. [2] Kim T, et al MRM 2005. [3] Petersen ET, et al. MRM 2006. [4] Hua J, et al. ISMRM 2009, Abs. 12. [5] Donahue MJ, et al. ISMRM 2009, Abs. 627. [6] Hua J et al. ISMRM 2009, Abs 1533.[7] Petersen ET et al. Neuroimage 2010.[8] Jenkinson M. et al. Neuroimage 2002. [9] Shiino et al. JCBFM 2003.