The effects of basal vascular tone on hypercapnic and hypocapnic cerebrovascular reactivity: implications for clinical autoregulation studies.

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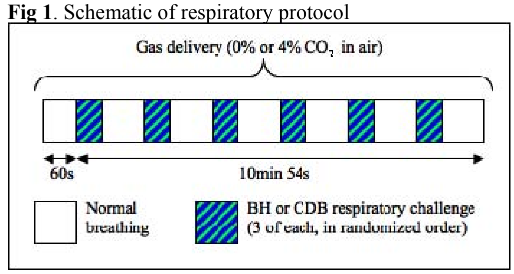
Introduction. Cerebrovascular reactivity (CVR) response to arterial gas tensions can offer insight into the compliance of blood vessels [1] and may be useful for experimentally simulating conditions of hemodynamic compromise in patients with carotid artery disease. Specifically, these patients may exhibit abnormalities in several vascular characteristics in response to reduced cerebral perfusion pressure, including autoregulatory vasodilation to compensate for reduced cerebral blood flow (CBF) in affected perfusion territories [2]. However, it is unclear how such baseline changes in cerebral blood volume (CBV) and/or CBF influence the BOLD reactivity measure. Here, we use BOLD fMRI and CO_2 inhalation in healthy volunteers to understand how an increase in basal vasodilation influences the BOLD CVR to both a vasoconstrictive deep breathing task and vasodilatory respiratory challenge. The hypothesis to be investigated was that increased basal CO_2 (and hence CBF and CBV) may attenuate the dilation CVR response, similar to the reduction in the HRF amplitude observed by [3] during neuronal stimulation and 5% CO_2 inhalation, while not having an affect on the constriction CVR response. This divergence would indicate that the two CVR measurement techniques reflect different vascular changes.

Fig 1. Schematic of respiratory protocol



Methods. ***Data acquisition***. Healthy volunteers (n=6) were scanned at 3.0T (Siemens) using body coil RF transmit and 12-channel head coil RF receive. Whole-brain BOLD fMRI data were collected with gradient-echo EPI (TR/TE/α=1500ms/38ms/73°, 3.5x3.5x4.0 mm^3). A structural image was also obtained for co-registration and mask generation (MPRAGE: TR/TI/TE=1778/900/4.4 ms, 1.7x1.7x2.0 mm^3). Two different baseline vascular conditions were created using inhalation of either 0% or 4% CO_2 in humidified air. A two-source gas delivery system was designed to allow for instant switching of the gas supplied to a non-rebreathing reservoir bag and face mask covering the mouth and nose of the subject. During each of the baseline conditions, subjects were instructed with visual cues to perform hypercapnia-inducing (vasodilatory) respiratory challenges (three blocks of 15 second breath-holds) or hypocapnia-inducing (vasoconstrictive) respiratory challenges (three blocks of Cued Deep Breathing [4]). During the first inhalation of the CDB challenge, the gas supply was switched to normal air for 2 breaths to facilitate a hyperventilation-related decrease in CO_2 levels. Three repetitions of each breathing challenge were administered, in a randomized order, interleaved with 90 seconds of normal breathing. A schematic of the protocol is shown in Fig. 1. Respiration was monitored using a bellows system, and a nasal cannula was inserted underneath the mask to continuously sample the O_2 and CO_2 content of expired air (BIOPAC MP150). ***Analysis***. BOLD data were corrected for motion, slice timing, and drift artifacts, before being spline-interpolated to a temporal resolution of 0.25 seconds. The starting time for each breathing challenge was identified using the bellows trace. For both BOLD datasets, mean CDB- and BH-response curves were calculated for every voxel by averaging the voxel timecourse within a 75-second window following the start times of the appropriate challenges. This mean response curve was smoothed (Gaussian kernel 9s) and the maximum or minimum signal change was measured for the BH or CDB data, respectively. The baseline value was calculated as the average BOLD signal in the 20 seconds preceding the challenges. The four resulting maps of %BOLD signal change were normalized to the mean end-tidal CO_2 change observed for the challenge type and baseline condition to create the traditional CVR maps for BH and CDB methods at 0% and 4% CO_2 inhalation. Finally, the structural image was segmented using FAST [5] to create a gray matter mask that was aligned to the maps, a loose threshold CVR<1.0 was applied to remove edge and other artifactually enhanced voxels, and CVR=%BOLD change / $etCO_2$ was calculated within the mask.

Fig 2.Average BOLD timecourse for 1 subject during 4% CO_2; timings for 6 challenges are indicated; timings for 6 challenges are indicated in red (BH) and blue (CDB).

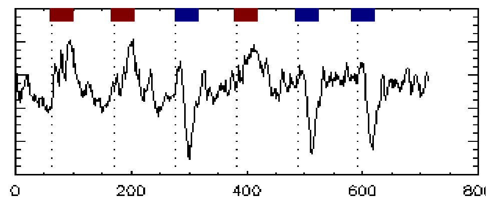
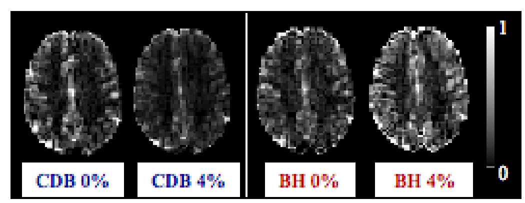
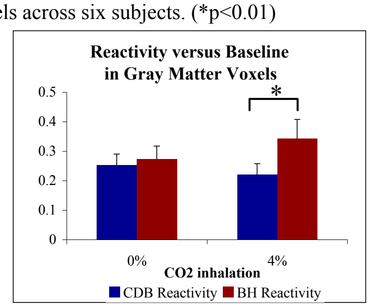


Fig 3. One slice from whole-brain CVR maps made using CDB and BH responses during 0 and 4% CO_2 inhalation for 1 subject prior to gray matter masking.



Results. A representative BOLD timecourse and normalized CVR maps for one subject are displayed in Figs. 2 and 3. Inhalation of 4% CO_2 caused a mean increase in $etCO_2$ of 5.83±1.66 mmHg. The CDB and BH derived CVR measurements (Fig. 4) are statistically indistinguishable during 0% CO_2 inhalation, but are significantly different during 4% CO_2 inhalation (paired t-test, $p<0.01$). The mean correlation across six subjects between un-masked CVR maps derived from the same challenge type during different gas mixture inhalations was R^2=.35±.07 for BH data and R^2=.50±.10 for CDB data; this effect was statistically significant in a paired t-test ($p<.05$).

Fig 4. Mean CVR measured in gray matter voxels across six subjects. (*p<0.01)



Discussion. Contrary to the attenuation effect observed in neuronal activation hemodynamics, the BOLD response to breath holding was amplified during inhalation of 4% CO_2. The CDB challenge, which causes a transient constriction response, was not significantly different in the 0% and 4% CO_2 conditions, although there is a trend in the subjects indicating a possible attenuation effect. These results support some clinical findings [6], where it is observed that the blood volume response to breath holding is increased in the symptomatic hemisphere of stenosis patients. The greater correlation observed in the CDB data may indicate the CDB challenge is a more reproducible technique, or that the amplification of the BH response is heterogeneous across the brain. Because the two respiratory challenges are affected differently by the CBV and CBF changes induced by CO_2 inhalation, they may offer complementary or more robust information about the status of patients' basal vascular tone and health when used together.

References:[1] Shiino *et al* 2003; [2] Derdeyn *et al.* 2002; [3] Cohen *et al*. 2002; [4] Bright *et al*. 2009; [5]Zhang et al. 2000; [6]Donahue *et al*. 2009.