An Alternative Technique for Measuring Cerebrovascular Reactivity; Comparing Cued Deep Breathing Hypocapnia with Inspiration of Carbon Dioxide

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Introduction

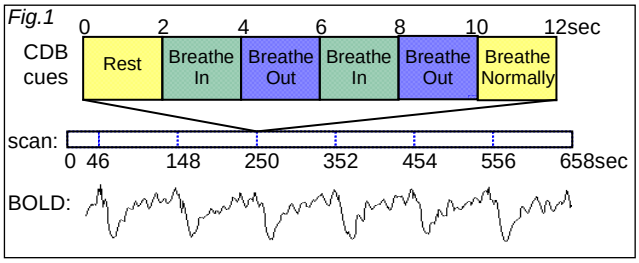
The characterization of cerebrovascular reactivity (CVR) to changes in arterial gas tensions can offer insight into the health and functionality of a subject's vasculature. While there exist several techniques for measuring vascular reactivity (e.g. TCD, PET, and SPECT) blood oxygenation level-dependent (BOLD) functional MRI offers whole brain information with high spatial resolution while using an endogenous contrast mechanism that obviates the need for invasive and radioactive methods. In 2003, Shiino et al. [1] examined the relative diagnostic abilities of CVR measurements acquired with breath holding BOLD fMRI and SPECT in patients with vascular abnormalities. The BOLD results showed good agreement with the more clinically established SPECT results and, surprisingly, were determined to be less ambiguous in identifying regions with impaired reactivity when examined by expert assessors. Nevertheless, the standard methods for manipulating gas tensions in reactivity studies, namely breath holding and administration of elevated CO_2, are not always feasible in a clinical setting. Recently we introduced a novel respiratory technique of cued deep breathing (CDB) which induced a robust BOLD signal decrease [2]. This task is much more suitable for patient populations, and the strong and short-lived BOLD change additionally allows for voxelwise characterization of the heterogeneous timing of this response. While we hypothesize that the BOLD signal decreases caused by the CDB task are due to the subject briefly becoming mildly hypocapnic, we wished to study how the CDB task quantitatively relates to gas tension changes or traditional hypercapnic methods. In this study, we directly compared the CDB task with a CO_2 challenge to better understand the changes in $PaCO_2$ caused by CDB and to gauge the reliability of reactivity measurements made with this simple method.

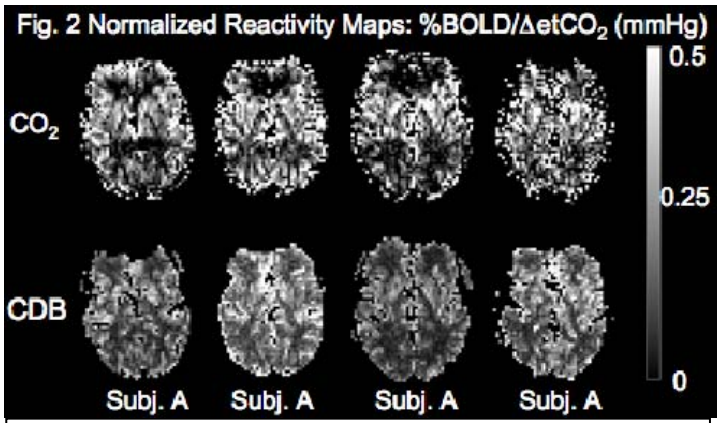
Methods

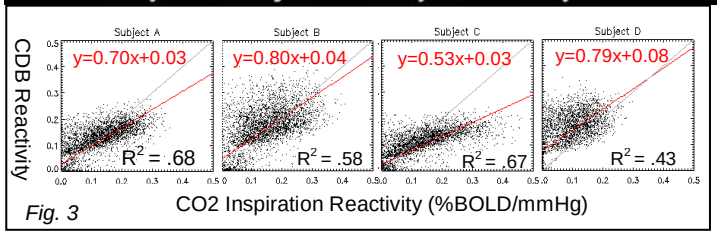
Eight volunteers (3 female, aged 23-32 years) were scanned with a 3 Tesla Siemens TIM Trio scanner using a gradient-echo EPI sequence (TR/TE=1250/35ms, FOV=225mm, resolution=3.5x3.5x5mm) and a 12 channel receive coil. Motion and slice timing corrections were performed using FSL. The CDB task and scanning paradigm are illustrated schematically in Fig. 1. In addition to the CDB paradigm, subjects also underwent a hypercapnia challenge: a mixture of 4% CO_2 in humidified air was supplied in two one-minute epochs using a close-fitting mask covering both the mouth and nose of the subject (Hans Rudolph Inc., Kansas City MO USA, 8920 Series), interleaved with one-minute periods of normal air delivery. The mask was connected to a filter and a large (10cm diameter, 2m long) open-ended tube acted as an exhaust path to minimize re-breathing of expired gases. For both paradigms, a port on the filter allowed continuous monitoring of respiratory composition using a CO_2 analyzer (Model CD-3A, AEI Technologies, Pittsburg, PA, USA). End-tidal values, known to well represent the arterial CO_2 content [3], were extracted using code developed in IDL. The BOLD signal timecourse of each voxel was interpolated using splines to a temporal resolution of 0.3 seconds. The starting times of the six breathing tasks were located using the trace from the gas analyzers. The interpolated BOLD timecourses in a 50 second window following the six CDB trials (located as described above) were averaged on a voxelwise basis, and this mean response curve was smoothed before the timing and magnitude of the signal minimum was identified. From these results, whole-brain reactivity maps (normalized to the mean end-tidal change across the 6 trials) were created. The 4% CO_2 gas challenge data were only analyzed for percent signal change, as the prolonged hypercapnic state did not result in the sharp BOLD signal changes that are required for robust temporal characterization. The BOLD signal in the second half of each CO_2 block was averaged and compared to the signal in the baseline periods for each voxel, and normalized using the end-tidal data to create traditional reactivity maps in units of % BOLD change per mmHg CO_2 change.

Table 1: End-tidal CO_2 levels (mmHg)

	CDB Paradigm		CO_2 Paradigm	
	Baseline	CDB	Baseline	4% CO_2
A	31.0±1.4	24.3±1.1	33.7±0.9	38.1±0.5
B	30.1±0.4	26.3±0.7	29.6±0.7	33.7±0.2
C	35.0±0.7	28.0±1.1	34.6±0.6	37.1±0.4
D	34.7±1.8	29.2±2.1	34.7±0.7	40.2±0.4







Results

vFour out of eight datasets allowed for comparison of reactivity maps between CDB and CO_2 inspiration methods, and thus offer a "proof of principle" that the CDB task is a viable method for reactivity determination. In these four subjects, the CDB task caused an end-tidal CO_2 decrease of between 3.90±0.74 and 6.99±1.25 mmHg for the six repetitions. The end-tidal levels returned to baseline after approximately three breaths. A comparison of the end-tidal effects in the deep breathing and 4% CO_2 challenge is given in Table 1. Fig. 2 shows slices from the reactivity maps created with both methods and accompanying scatter plots that show the correlation between the normalized reactivity measured with the two methods. Four subjects were not successful in reaching the end-tidal CO_2 changes necessary to create the strong BOLD signal changes that we expect based on previous studies. This is most likely a reflection of the oppressive environment caused by the mask, filter, and tubing system: deep breathing is hindered by the resistance inherent to the filter, and while the tubing system is designed to assist in the flushing out of expired air, a portion of the expired volume will inevitably remain in the mask environment. The increased levels of CO_2 in this "dead space" is likely to prevent the subject from becoming as hypocapnic as compared with our initial research performed with a nasal cannula to monitor breathing. This suggests that the CDB task, like all respiratory challenges, requires careful consideration of the scanning environment, from pre-scan training through to details of task execution.

Conclusions

The Cued Deep Breathing task causes changes in end-tidal CO_2 that are of the same order of magnitude as a traditional CO_2 challenge, although the effect is short-lived and the end-tidal values show high inter- and intra-subject variability. This mild hypocapnia task causes a BOLD signal change that enables whole-brain mapping of cerebrovascular reactivity. This study suggests that this simpler respiratory task can offer similar diagnostic information in situations where gas inspiration and breath holds are not ideal.

References: [1] Shiino et al. *JCBFM*. 2003. Jan23(1); [2] Bright et al. *ISMRM 2008* poster 2347. [3] McNulty et al. *J.Clin.Mon.Comp.* 1989. April 6(2)