Test-retest reproducibility of the BOLD response to a hypercapnic challenge

Bryon A. Mueller[1], Nicholas Evanoff[2], Kara L. Marlatt[2], Justin R. Geijer[3], Kelvin O. Lim[1], and Donald R. Dengel[2]

[1]Department of Psychiatry, University of Minnesota, Minneapolis, MN, United States, [2]School of Kinesiology, University of Minnesota, Minneapolis, MN, United States, [3]Department of Health, Exercise and Rehabilitative Sciences, Winona State University, Winona, MN, United States

Target Audience: Researchers and clinicians interested in using $P_{et}CO_2$ manipulation and BOLD imaging to measure CVR.

Purpose: Cerebrovascular reactivity (CVR) is the change in cerebral blood flow in response to a vasoreactive stimulus. Impaired CVR occurs in a number of cerebrovascular diseases; however, impaired CVR is difficult to measure clinically. Increasingly, researchers are using blood oxygen level-dependent (BOLD) MRI and vasodilatory stimuli to measure CVR. While several stimuli (e.g. breath hold, inhaling a fixed concentration of CO_2) have been used to measure CVR, each has issues limiting their use. The recent development of a computer-controlled sequential rebreathing device[1] capable of independently controlling end tidal CO_2 ($P_{et}CO_2$) and O_2 ($P_{et}O_2$) has enabled researchers to deliver a controlled CO_2 stimulus which induces faster and more stable CVR changes compared to other methods. This study examined the reproducibility of the measurement of CVR under hypercapnic (HC), iso-oxic (IO) conditions.

Methods: Eleven healthy subjects (6 female, age 26.5±5.7 years) were scanned twice on two visits separated by at least 3 days. Subjects were asked to abstain from caffeine consumption for 12 hours and vigorous exercise for 24 hours prior to scanning. All scanning utilized the Siemens 3T Skyra Connectome magnet[2] and a 32-channel receive only head coil. Each scan visit consisted of a T_1 weighted anatomic image (MP-RAGE, 1mm^3 voxel), a field map, and two sequential BOLD scans (GE-EPI, 3.4x3.4x4mm) acquired during HC challenge. Subjects were fitted with a specialized breathing circuit and synchronized their breathing to 12 breaths per minute. Each BOLD scan included an 18 minute HC challenge during which target $P_{et}CO_2$ followed the square wave pattern shown in green in Figure 1. $P_{et}O_2$ values were targeted to 100 mmHg throughout the scan. To determine within day reproducibility, participants underwent consecutive BOLD scans on each testing day. Image processing was performed using FSL tools and custom MATLAB scripts. Brain extraction and 3-compartment tissue segmentation was performed on the T1. BOLD image processing consisted of brain extraction, distortion correction and motion correction with no additional temporal or spatial smoothing applied. Gray matter masks were created in BOLD space using the aligned PVE map from the T1 segmentation with a 50% threshold and the mean gray matter voxel value for each volume was determined. A linear detrend was applied to the BOLD and $P_{et}CO_2$ time courses and then linear regression was used to compute CVR (%ΔBOLD / Δ$P_{et}CO_2$ mmHg). CVR was computed independently for the first and second $P_{et}CO_2$ square change, using the surrounding baseline. Test-retest reproducibility of CVR was computed for within scan, within day and between day using intraclass correlation coefficient (ICC) and coefficient of variations (CV).

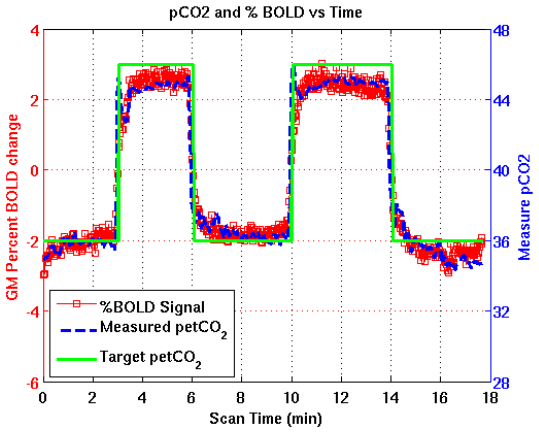

Figure 1 Example scan showing target petCO2, measured petCO2, and % BOLD change from 1 scan.

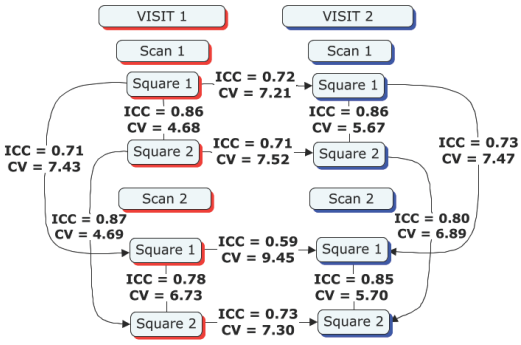

Figure 2 CVR test-retest reliability CV and ICC values.

Results: Subject baseline $P_{et}CO_2$ levels did not differ between day 1 and 2 (31.2±0.8 and 31.8±1.1 mmHg, P=0.5) and no statistical difference was found in mean CVR between days, between scans or within scans. The CV for CVR across like comparisons ranged from 4.7-6.7% for within scan, 4.7-7.5% for within day and 7.2-9.5% for between days. ICC values for CVR ranged from 0.78-0.86 for within scan, from 0.71-0.87 for within day, and from 0.59-0.73 for between days. The complete CVR test-retest reproducibility CV and ICC values for all like combinations of within scan, within day and between day measures are shown in Figure 2.

Discussion: The objective of this study was to examine the reproducibility of CVR measured using a HC lasting 3 or 4 minutes with $P_{et}CO_2$ set to about 10 mmHg above baseline with $P_{et}O_2$ clamped at 100 mmHg. Similar protocols have been used in previous CVR studies of clinical populations[3,4,5,6]. Within scan and within day reproducibility reflects the reliability of the method. For this study within scan reproducibility is in the excellent range (ICC > 0.75) and between scan reproducibility (e.g. square 1/scan 1 vs. square 1/scan 2) is in the very good to excellent range (ICC > 0.71). Between day reproducibility has been attributed to a combination of method reliability and subject "physiological contribution"[7]. CVR reproducibility between day one and day two (separated by at least 3 days) is found to be in the very good range (ICC > 0.70) in 3 of 4 cases. The lower between-day reproducibility may reflect normal variation in day-to-day physiologic difference within subjects. The within and between day ICC values are reproducible based on biostatistics standards.[8]

Conclusions: CVR measured using a controlled, iso-oxic and hypercapnic stimulus using two periods of increased $P_{et}CO_2$ is reproducible within scan, within day, and between days. The good reproducibility observed in this study is due in part to repeatability of the iso-oxic, HC stimulus provided by the computer-controlled sequential rebreathing device used in this study[4,6]. The use of CVR to investigate differences between groups of people as well as to study individuals longitudinally will continue to increase as these methods are shown to be reproducible.

References: [1]RespirAct™, Thornhill Research, Inc., Toronto, Canada; [2]http://www.humanconnectome.org/; [3]Stroke 2008, 39, 2021-2028; [4]MRM 2010, 64, 749-756; [5]PloS one 2012, 7(11), e47443; [6]J Physiol 2013, 591(23), 5809-5821; [7]JMRI 2010, 31(2), 298-304; [8]Rosner B. 2006. Fundamentals of Biostatistics. 6th ed. Belmont.

This work was supported by: University of Minnesota Grant-in-Aid, P41 EB015894, P30 NS076408, U54 MH091657