Differences in cerebrovascular reactivity in males versus females obtained using BOLD MRI and alternating states of end-tidal CO2

A. Kassner[1], J. Poublanc[2], G. Tomlinson[1], D. Mikulis[2], A. Crawley[2]

[1]Medical Imaging, University of Toronto, Toronto, Ontario, Canada, [2]Medical Imaging, The Toronto Western Hospital, Toronto, Ontario, Canada

Introduction: Combining inhaled CO_2 manipulation with BOLD MRI is a promising method for assessing regional differences in cerebrovascular reactivity (CVR) which is a measurement of the brain's autoregulatory capacity. This becomes important for the assessment of vascular disorders in which autoregulation is compromised or exhausted such as in moyamoya disease or carotid stenosis/occlusions. The characterization of these pathophysiological conditions in the cerebral circulation, however, requires the knowledge of potential physiological gender-dependent differences in CVR. The objective of this study was to evaluate gender differences in CVR in normal subjects using quantitative CVR measurements by correlating BOLD MR signal intensity with square wave changes in end-tidal pressure of CO2 (p_{ET} CO_2).

Materials and Methods: Ten healthy male (age range 25 - 42 years) and 9 healthy female (age range 21-38 years) volunteers were imaged on a 1.5T GE Signa MR system 4 times (2 sequential runs on day 1 and 2 sequential runs on a separate day 1-2 weeks later) using a rebreathing circuit as previously described [1]. Each subject was placed inside the scanner and the rebreathing device was applied. Scanning was performed using a standard single-shot BOLD protocol with a spiral read out (TE=40ms, TR=2240ms, FA=85°, FOV=20mm). Scanning duration for each run was 12 minutes for an acquisition of 320 volumes. Each volume contained 28 slices and spatial resolution of the BOLD data was approx 3 x 3 mm with a slice thickness of 4.5mm. In addition, high resolution T1 weighted images were acquired for co-registration purposes. Changes in $p_{ET}CO_2$ were achieved by controlling the subjects inspired gases with the aid of a nose clip, a mouthpiece, the rebreathing circuit, and a gas sequencer. To ensure that end-tidal gases are representative of lung gas concentrations, subjects were instructed to breathe deeply during the test. The test itself consisted of eight cycles of hypercapnia (45sec at ~ 50mmHg) interspersed with eight cycles of hypocapnia (45sec at ~ 30mmHg) all of which was regulated by an automated sequencer. Hypercapnia was induced by administering a gas mixture of 8% CO_2/92% O_2 at 14L/min for 15 sec and maintained at plateau for a subsequent 30 sec by reducing gas flow to 1.5-2 L/min of O_2. During the plateau phase, the decreased inflow of fresh gases resulted in rebreathing of previously exhaled gases contained in the expiratory reservoir tube. Intervals of low CO_2 were achieved by supplying subjects with 15sec of high flow (16-18 L/min) of 100% O_2 and maintained by O_2 flow at a rate of 12-14 L/min. Partial pressures of end-tidal CO_2 ($p_{ET}CO_2$) and O_2 ($p_{ET}O_2$) were monitored continuously using a commercially available capnograph and recorded digitally at a sampling rate of 60Hz/channel. After completion of the measurement, the collected $p_{ET}CO_2$ data was reduced to one measure of $p_{ET}CO_2$ per breath and correlation analysis with the BOLD data was performed. Prior to this, the BOLD data was co-registered to compensate for motion artifacts. Signal of the whole brain was used as a reference to determine the shift needed to bring the CO_2 and the MR data sets in phase. Once in phase, CVR maps were calculated on a pixel by pixel basis from the slope of the regression of the percentage change of MR signal on the $p_{ET}CO_2$. This provides a measure of reactivity expressed in units of % Δ MR signal/mmHg $p_{ET}CO_2$. A variance components analysis was used to estimate variability in reactivity between runs, different days and subjects. Reproducibility was quantified using the interclass correlation coefficient (ICC). Differences between mean reactivity of males and females were assessed using the Wilcoxon rank sum test.

Results: Averages of the 4 BOLD signal changes for males ranged from 0.10 to 0.21 %Δ MR signal/mmHg $p_{ET}CO_2$ (mean=0.157, SD=0.029). For females, these values ranged from 0.098 to 0.161 %Δ MR signal/mmHg $p_{ET}CO_2$ (mean=0.123, SD=0.022). The mean value for males is statistically higher than that for females (p=0.01) – see figure1. Results for the day to day variation of runs for both genders show excellent reproducibility with an ICC=0.89 (95% CI:0.72-0.97) for males and an ICC=0.96 (95% CI:0.91-0.99) for females. These values are for the whole brain. For correlated values above r=0.3, the ICC=0.95 (95%CI:0.86-0.99) for males and 0.92 (95% CI:0.81-0.98) for females. Within a session, there is approximately a 95% chance that repeated measures for entire brain values on a subject would lie within ±0.02 %Δ MR signal/mmHg $p_{ET}CO_2$ of each other (0.017 for females and 0.024 for males). For values above r=0.3, the measurement error is slightly higher in the absolute sense. Here, 95% of repeated reads should lie within ±0.04 %Δ MR signal/mmHg $p_{ET}CO_2$ of each other (0.036 for females and 0.41 for males). CVR maps of 2 subjects (1 male, 1 female) are shown in figure 2.

Discussion: This study shows excellent reproducibility and demonstrates differences in CVR between males and females in the order of 27.6% for the entire brain. These differences may have important implications for the assessment of therapeutic interventions using CVR and need to be further investigated.

References: 1. Vesely et al. MRM 2002

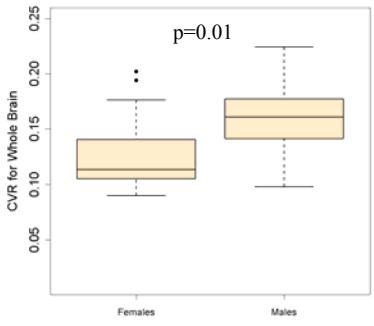

Fig.1: Distribution of CVR for males and females

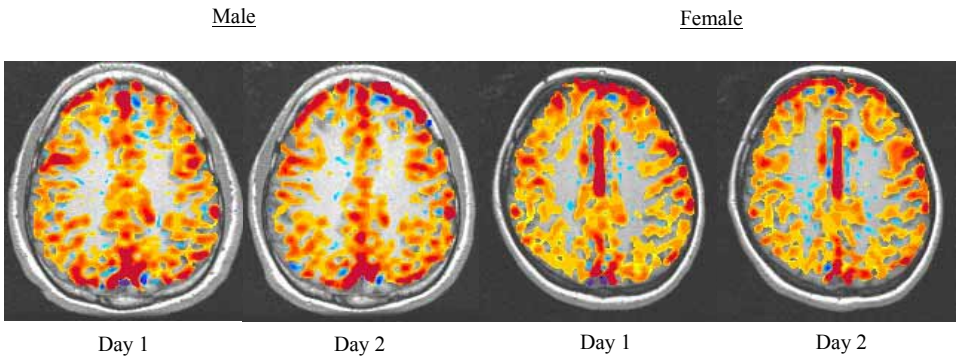

Fig.2: CVR maps of a male and female volunteer obtained on 2 different days