Reproducibility of M, CMRO2 and OEF measurements using QUO2 MRI and dual-echo pCASL

Isabelle Lajoie[1], Felipe B Tancredi[1], Danny J Wang[2], and Richard D Hoge[1]
[1]*Centre de recherche de l'IUGM, Montreal, Quebec, Canada,* [2]*Neurology, University of California, Los Angeles, CA, United States*

Target audience: Researchers interested in calibrated MRI and in imaging of cerebral metabolic rate of O_2 consumption ($CMRO_2$) by MRI.

Purpose: Recently, several groups have introduced a method, which allows the noninvasive imaging of resting cerebral metabolic rate of O_2 consumption ($CMRO_2$) by MRI[1,2,3]. The approach described by our team, dubbed QUO_2, is based on a hybrid calibration of the BOLD signal that includes the use of both hypercapnia (HC) and hyperoxia (HO) as iso-metabolic manipulations. During the latter conditions, BOLD and CBF responses are measured simultaneously using an implementation of pCASL that includes a dual-echo readout. The resultant end-tidal O_2 (ETO_2), fractional BOLD change, and fractional CBF change are put into the Generalized Calibration Model (GCM)[4], yielding a system of two equations with two unknowns: the BOLD calibration parameter *M* (extrapolated maximum BOLD signal increase when venous saturation approaches 100%) and Oxygen Extraction Fraction (OEF; the fraction of delivered oxygen that is consumed). $CMRO_2$ can then be determined by multiplying O_2 delivery, itself the product of CBF and arterial O_2 content, with the OEF. In a parallel study, our group has demonstrated the reproducibility of the ETO_2 and $ETCO_2$ traces during the respiratory manipulation, as well as that of the resting CBF, hypercapnia-induced change in CBF, and percent change in BOLD during hypercapnia and hyperoxia. The goal of the present study was to assess the test-retest reliability of the QUO_2 outputs *M*, OEF_0 and $CMRO2_0$, on a group of healthy control subjects, to aid in calculation of statistical power in future applications.

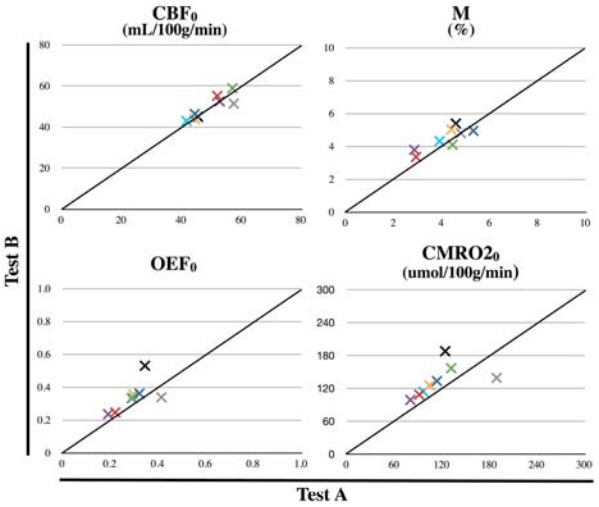

Figure 1. Correlation plot of CBF_0 and QUO_2 outputs in GM

Methods: Eight healthy participants (25-40 years), were imaged on a 3 T Siemens Tim Trio scanner using the vendor's 32-channel receive-only head coil. Each participant was scanned twice (Test A and B) within 24 hours. Each scan session included an anatomical, $1mm^3$ MPRAGE acquisition (TR/TE/flip angle = 2.3s/3ms/9°, 256x240 matrix), and one pCASL sequence providing simultaneous measures of BOLD and CBF using dual-echo readouts (labeling duration = 2s, post-labeling delay = 0.9s, 3255 Hz/px bandwidth, TR/TE1/TE2/alpha = 4.12s/8.5ms/30ms/90°, GRAPPA factor = 2, partial sampling of k-space = 7/8, $4.5mm^2$ in-plane resolution, advanced phase correction option, 21 slices with 4.5mm thickness, 10% gap,). Subjects were fitted with a breathing circuit designed by our group that allows precise control over fractional concentration of inspired CO_2 and O_2. We used a schedule for respiratory manipulations described in [2] that includes two 2-minute blocks of hypercapnia and two 3-minute blocks of hyperoxia, interleaved with normocapnia and normoxia for a total of 18 minutes. During the hypercapnia blocks a 5% CO_2 / Air mixture was administered at 20L/min while in hyperoxia blocks we have administered a 10L/min of medical air and 10L/min of 100% O_2, resulting in a concentration of approximately 61% O_2. ETO_2 and $ETCO_2$ were continuously monitored using a BIOPAC MP150 system. A linear model described in [5] was used to obtain values of ETO_2 at baseline and during both HC and HO. Data was analyzed with Neurolens and FSL software. Motion correction was applied on the series, then the BOLD and ASL series were isolated using surround subtraction. A GLM fit was applied to obtain response estimation to HC and HO. Conversion of ASL to CBF in physiological units (mL/100g/min) was performed as in [6]. Voxels considered to be from large vessels (CBF_{HO} < -50 mL/100g/min; $\Delta\%BOLD_{HC}$ > 10%) and BOLD artifact due to O2 inhalation ($\Delta\%BOLD_{HO}$ < -5%) were identified and removed in the motion corrected raw series. We then performed spatial filtering (6mm FWHM 3D Gaussian kernel) and corrected for the downward effect of the removed voxels. Grey-matter (GM) averaged values were computed using a probability mask (obtained from the anatomical scan) thresholded to 50%. Because of the low SNR inherent to ASL and the almost null CBF decrease at hyperoxia of 61% O_2, we used a fixed estimate of 0% for $\Delta\%CBF_{HO}$. We then input the following values to the GCM: the ETO_2 during baseline and activation, CBF_0, $\Delta\%CBF_{HO/HC}$ and $\Delta\%BOLD_{HC/HO}$. Using either the maps of the latter parameters, or their GM-averaged values as inputs, we were able to obtain the corresponding maps or GM values of resting OEF, *M* and $CMRO_2$. As a measure of reproducibility, we used the inter-session coefficient of variation (CV), which is a variability expressed as a percent of the mean value, as described in [7]. The reproducibility has been verified at both subject and group level.

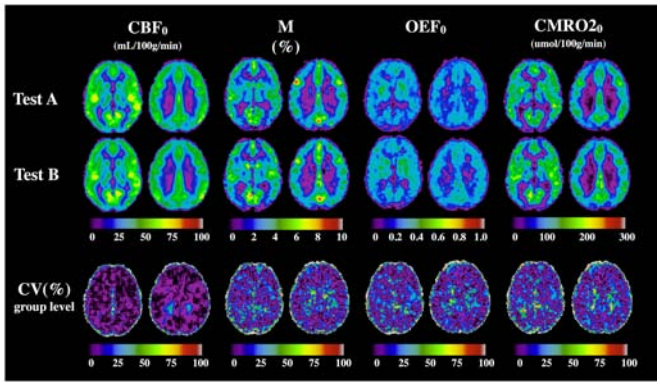

Figure 2. Two different slices of group-average maps for Test A and Test B, with corresponding CV% maps computed at group-average level

Results: Plots of correlation between GM values of CBF_0, *M*, OEF_0 and $CMRO2_0$ in Test A and B are shown in Figure 1. Values are plotted around the identity line indicating a good reproducibility of the measurements. Table 1 shows the group-average Test A and Test B in GM and corresponding inter-session CV(%) at the subject and group level. Figure 2 shows group-average maps of Test A and Test B with the corresponding CV maps computed at the group level. Maps were registered to MNI space and two slices are compared. The group-average maps demonstrate the reproducibility of anatomical patterns in the measured parameters. As expected, CBF_0 exhibits better reproducibility, likely due to the fact that it is a direct measurement whereas *M*, OEF_0 and $CMRO2_0$ integrate multiple measures, including ratio images which are particularly vulnerable to noise in the denominator.

	CBF_0 (mL/100g/min)	M (%)	OEF_0	$CMRO2_0$ (umol/100g/min)
Mean A (± SE)	49 ± 2	4.16 ± 0.31	0.30 ± 0.02	116 ± 12
Mean B (± SE)	50 ± 2	4.48 ± 0.24	0.34 ± 0.03	133 ± 10
CV (%) subject level	3.5	10	15	17
CV (%) group level	0.21	5	10	9

Table 1. Group-average GM values with corresponding inter-session CV at subject level and group level

Conclusion: We have assessed test-retest reliability of the QUO_2 method, demonstrating good reproducibility of all output parameters at a readily achievable cohort size. In future work, we will focus on further optimization of analytical methods to better manage noise propagation from input measures. In addition, we will implement equivalent scanning protocols for MRI scanners from other vendors, and verify that we can obtain reproducible results across different sites and scanners. Funding support from the CQDM, under the FOCUS program, is gratefully acknowledged.

References: [1] Gauthier, CJ, Hoge, RD. NeuroImage 2012;63:1353-63 [2] Bulte, DP, et al. NeuroImage 2011;60:582-91 [3] Wise RG, et al. NeuroImage 2013;83:135-47 [4] Gauthier, CJ, Hoge, RD. HBM 2013;34(5):1053-69 [5] Tancredi FB, Hoge RD. CBFM. 2013;33:1066-74 [6] Wang J, et al. JMRM 2003;50:599–607 [7] Chen Y, Wang DJJ, Detre JA. JMRI 2011;33(4):940-49