# Reproducibility of BOLD and CBF responses to fixed step changes in inspired $O_2$/$CO_2$ using dual-echo pCASL

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***Target audience***: Researchers interested in calibrated MRI and fMRI measures of cerebrovascular reactivity to respiratory gases.

***Purpose:*** Functional MRI of CBF and BOLD responses to blood gas manipulations have been used to characterize reactivity of the cerebral vasculature[1], and to calibrate physiological models allowing estimation of cerebral oxygen consumption[2]. Such manipulations are usually achieved using breathing maneuvers that induce changes in respiratory end-tidal (ET) levels, which reflect arterial blood gas content[3]. A common way to induce hypercapnia (HC) and hyperoxia (HO) has been to administer air mixtures containing $CO_2$ or supplemental $O_2$ through loosely fitting clinical oxygen masks used in respiratory therapy. A limitation of this approach is the poor control over the composition of gases actually inspired by the participant, which hampers reproducibility of the respiratory stimuli and related fMRI measures. More sophisticated alternatives include the use of mouthpieces + nose clips in place of the oxygen mask, or sealing the edges of standard oxygen masks with adhesive tape, but these solutions can be uncomfortable for the subject. We have designed a breathing circuit that provides improved control over the inspired doses using a comfortable mask that is easily put on and removed, and which provides a backup supply of room air if the flow of medical gases is interrupted. The objective of this study was to assess the test-retest reliability of BOLD and CBF responses to fixed step changes in inspired $O_2$ and $CO_2$ levels, using a dual-echo pCASL sequence to simultaneously image blood flow and oxygenation.

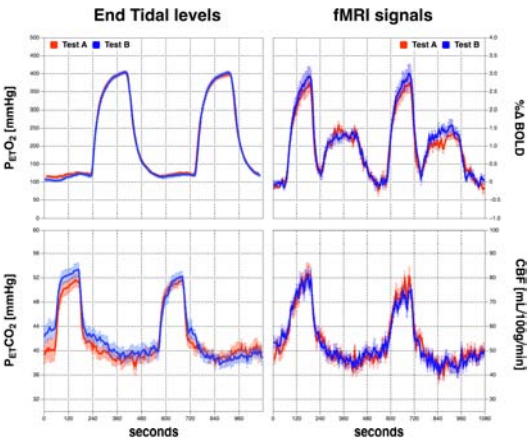


Figure 1 – Average traces of $O_2$/$CO_2$ during the manipulations and related pCASL measures

***Methods:*** Eight subjects (age 25-40) were scanned twice (Tests A and B) within a 24h interval and had BOLD and CBF measured during a respiratory manipulation including HC and HO. Images were acquired using a Siemens 3T TIM Trio scanner using the vendor's 32-channel head coil. After a high resolution anatomical acquisition (5min MPRAGE at $1mm^3$), a dual-echo pCASL sequence was used to obtain simultaneous measures of BOLD and ASL. The pCASL parameters were: label duration = 2s, post-label delay = 0.9s, labeling plane 10cm below the centre of image slab, TR = 4.12s and TE1/TE2 = 8.5ms/30ms. Readout consisted of a GRE-EPI scheme (GRAPPA factor of 2 and 7/8 partial sampling of k-space) imaging a total of 21 slices with 4.5mm thickness, 10% gap and at an in-plane resolution of $4.5mm^2$. For the respiratory manipulation we have adopted the 18-min schedule proposed by Bulte et al[4], interleaving two 2-min periods of HC stimulation with two 3-min periods of HO. An automated system, fabricated in-house, was used for the switching and mixing of gases to ensure reproducible timing of the gas administration schedule. During the baseline periods, subjects breathed air with atmospheric composition. To induce HC we switched the gas composition from medical air to a 5%-$CO_2$/air mixture. The gas mixture used to induce HO was obtained by combining equal amounts of 100% $O_2$ and medical air in the mixing chamber of our system prior to delivery. Gas delivery was achieved using an in-house breathing circuit affording precise control over the inspired doses. Respiratory gases were continuously monitored and recorded using a Biopac MP150 system. Baseline and change values for ET levels of $O_2$ and $CO_2$ were computed using a linear model as described in [3]. Images were analyzed using NeuroLens and FSL software packages. Image series were first motion corrected. BOLD and ASL signals separated using surround subtraction and responses were modeled using a GLM consisting of 1 regressor for each of the 2 hypercapnic/hyperoxic stimuli plus a 3rd degree polynomial to represent signal drift and baseline offset. Effect sizes of HC and HO were averaged to synthesize the HO/HC responses in a single value for each type of stimuli. ASL signals were converted to CBF in units of mL/100g/min as in [3]. Voxels presenting CBF responses lower than -50 mL/100g/min in HO, BOLD responses lower than-5% in HO and higher than 10% in HC were considered to be non-parenchymal and were excluded from further analysis. We then reanalyzed the data, this time applying spatial smoothing just after motion correction (6mm FWHM Gaussian kernel) but excluding the non-parenchymal voxels and compensating for downward bias introduced by their removal. To estimate the BOLD and CBF signal in grey-matter (GM) we have computed GM-weighted averages by averaging signals over a GM probability mask we obtained from segmentation of the anatomical scan (masks were thresholded at 50% and had non-parenchymal voxels removed). Lastly, we registered individual maps to the MNI 152 template and computed group-average maps for the different scan session, i.e. Tests A and B. As a measure of the reproducibility of our respiratory manipulations and fMRI measures in GM we have computed the inter-session coefficient of variation (CV) for these variables as in [5].

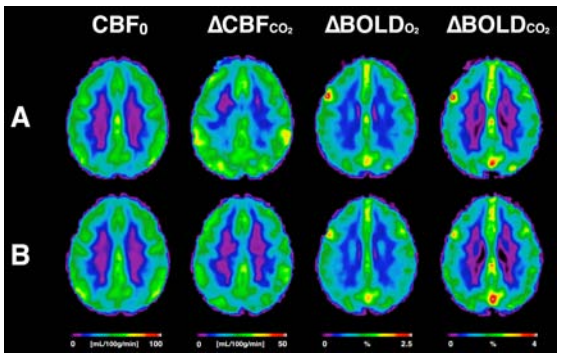


Figure 2 – Group-average maps for Tests A and B

***Results:*** Figure 1 shows group-average BOLD and CBF signals in GM (right column) obtained in Tests A and B (red and blue, respectively) along with the group-average traces of $O_2$ and $CO_2$ ET partial pressures (left column). Drifts have been removed from the BOLD signal. Error bars represent standard error (SE). Figure 2 shows group-average maps of baseline CBF, CBF response to HC and BOLD responses to both HO and HC. Table 1 shows a summary of ET levels and GM fMRI measures obtained in Tests A and B, and the inter-session CV expressed as a percent of the mean value. As expected, baseline (BSL) CBF and ET levels varied little between Tests A and B. While changes in ET $O_2$ were also very reproducible, changes in $CO_2$ exhibited a slightly higher CV. The BOLD and CBF responses we measured in both tests were generally consistent: for BOLD, CV values were below 10% and below 20% for CBF responses (which are expected to have lower SNR).

***Conclusion:*** Using a simple respiratory manipulation based on fixed compositions of inspired gases, we have achieved consistent changes in end-tidal gases and obtained pCASL measures of CBF and BOLD in GM that were robust and reproducible. Although we used an automated system for the switching and flow control of gases, the same results could have been obtained through the manual operation of standard clinical flow regulators. With manual switching of gases, comparable results should be attainable using commercially available respiratory apparatus at relatively low cost. We are currently implementing equivalent scanning protocols on MRI systems from other vendors, which should further facilitate the broader adoption of these methods. Funding by the CQDM is gratefully acknowledged

***References***: [1] Stroke 2008; 39:2021-2028. [2] NeuroImage 2012; 60(2): 1212-25. [3] CBFM. 2013; 33:1066-1074. [4] NeuroImage 2012; 60:582-591. [5] JMRI 2011; 33(4): 940-949.

| | ET levels | | | | fMRI measures | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | O2 | | CO2 | | CBF | | | | BOLD | | | |
| | BSL | Δ | BSL | Δ | BSL | Δ to CO2 | Δ/ΔCO2 | %Δ/ΔCO2 | %Δ to CO2 | %Δ/ΔCO2 | %Δ to O2 | %Δ/ΔO2 |
| | mmHg | mmHg | mmHg | mmHg | mL/100g/min | mL/100g/min | mL/100g/min/mmHg | %/mmHg | % | %/mmHg | % | %/100mmHg |
| A | 118 ± 3 | 281 ± 3 | 39 ± 1 | 11.8 ± 0.8 | 49 ± 2 | 27 ± 2 | 2.4 ± 0.2 | 4.9 ± 0.5 | 1.9 ± 0.2 | 0.17 ± 0.02 | 1.16 ± 0.04 | 0.41 ± 0.01 |
| B | 117 ± 4 | 285 ± 4 | 40 ± 1 | 12.1 ± 0.8 | 50 ± 2 | 25 ± 2 | 2.1 ± 0.2 | 4.3 ± 0.5 | 1.9 ± 0.2 | 0.17 ± 0.02 | 1.12 ± 0.03 | 0.39 ± 0.01 |
| %CV | 4.2 | 3.8 | 5.5 | 13.2 | 3.5 | 14.8 | 18.4 | 18.8 | 6.8 | 8.8 | 8.4 | 10.0 |

Table 1 – Summary of respiratory manipulations and GM-averaged pCASL measurements