Reproducibility of arterial spin labeling and blood-oxygen level dependent measures of cerebrovascular reactivity using a controlled cerebrovascular challenge

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Introduction: Cerebrovascular reactivity (CVR), the cerebral blood flow (CBF) response to a vasoactive stimulus, provides an additional tool for the clinical assessment of cerebrovascular disease[1]. MRI acquisition of regional CVR images is typically performed using relative blood-oxygen level dependent (BOLD) signal changes or arterial spin labeling (ASL) measures of CBF in response to experimental manipulation of CO_2. CVR imaging with BOLD provides an indirect measure of CBF changes that is dependent on multiple factors. Advantages of BOLD imaging include improved SNR (compared with ASL) and wide availability of BOLD sequences. Furthermore, the precise control of end-tidal PCO_2 ($PETCO_2$) via a computer-controlled, model-driven end-tidal prospective targeting (MPET) system can be used to improve the accuracy and reliability of BOLD-CVR imaging[2]. Clinical utility of ASL-based CVR measures may be improved with higher magnetic field strength, novel acquisition strategies, and use of a controlled cerebrovascular challenge. We hypothesized that ASL measures of CBF performed using a modified Look-Locker (LL) acquisition strategy at 3.0 T, in combination with a controlled CO_2 stimulus, would provide ASL-CVR values with similar reproducibility to BOLD-CVR values.

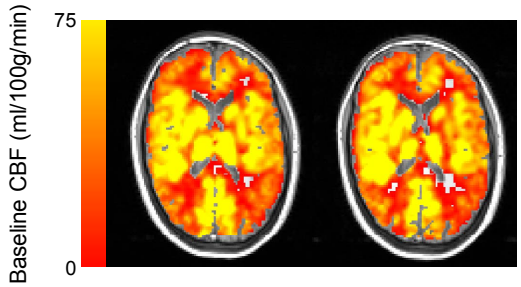

Figure 1. Representative test (left) and (right)ASL images of CBF collected at baseline $PETCO_2$ levels.

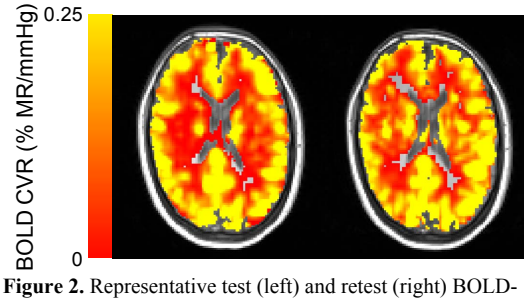

Figure 2. Representative test (left) and retest (right) BOLD-CVR images collected during square-wave $PETCO_2$ changes.

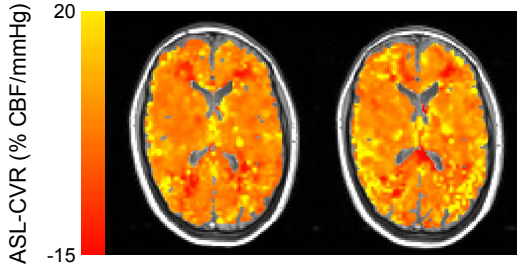

Figure 3. Representative test (left) and retest (right) ASL-CVR images collected during square-wave $PETCO_2$ changes.

Methods: Four healthy adult subjects (21 - 29 years old, 2 males, 2 females) were imaged on a 3.0 T Philips MRI scanner. $PETCO_2$ and $PETO_2$ targets were achieved using a MPET (RespirAct™, Thornhill Research Inc., Toronto, Canada)[3], which maintains $PETCO_2$ and $PETO_2$ levels in close agreement with arterial blood gas values[4] .We assessed long-term reproducibility by collecting test-retest BOLD-CVR and test-retest ASL-CVR measurements performed on two separate days, 2 weeks apart. BOLD-CVR measurements were acquired during four square-wave cycles of hypercapnia ($PETCO_2$ = 44 mmHg for 60 s) and normocapnia ($PETCO_2$ = 37 mmHg for 60 s). BOLD imaging parameters included: TE = 30 ms, TR = 2 s, FOV = 220 mm, matrix size = 64 × 64, SENSE = 1.8, slices = 25, slice thickness = 5 mm, volumes = 270, and scan time = 9 min. Perfusion-weighted (ΔM) ASL images were collected using a pulsed STAR labeling method (150 mm plane 30 mm inferior to the imaging slab) combined with a LL readout that sampled eight label delay times from 650 ms to 3450 ms. Imaging parameters included: FOV = 220 mm, matrix 64 x 64, number of slices = 9, slice thickness = 5 mm, SENSE = 2.3, temporal resolution = 8 s, and scan time = 9 min. Baseline CBF measurements were collected (30 averages) without $PETCO_2$ control; whereas, ASL-CVR measurements (68 averages) were collected during MPET square-wave cycling of $PETCO_2$, which was identical to the protocol used for BOLD-CVR imaging. Baseline CBF images were quantified by fitting the average ΔM images to the modified kinetic model described by Gunther *et al.*[5]. ASL-CVR was quantified by fitting average ΔM images collected at hyper- and normocapnia to the model separately. ASL-CVR was expressed as the percent CBF change per unit $PETCO_2$. To separate gray matter (GM) and white matter (WM) regions, we segmented high-resolution 3D anatomical images. Baseline CBF, BOLD-CVR and ASL-CVR images were then transformed to the anatomical images to extract mean GM and WM values. Reproducibility was assessed using the between-day coefficient of variation (CV).

Results: Test-retest images from a representative subject are provided for baseline ASL CBF (Figure 1), BOLD-CVR (Figure 2) and ASL-CVR (Figure 3). Mean baseline ASL CBF measures exhibited good between-day reproducibility for both the GM and WM regions (CV < 8 %, Table 1). Between-day BOLD-CVR measures in GM and WM had a CV < 19 % (Table 1), which was similar to the reproducibility of the ASL measures of the CBF reactivity to CO_2 (CV < 17 %).

Discussion: In this study, we demonstrated the feasibility of generating quantitative CVR images with an LL ASL approach in combination with MPET delivery of precise $PETCO_2$ transitions. By targeting specific $PETCO_2$ levels, ΔM images can be separately averaged at low and high CO_2 levels to improve the SNR for the perfusion model fit. The % CBF reactivity to CO_2 in this study (6.5 % CBF / mmHg) was greater than a previous report using ASL at single inversion time of 1.7 s (4 % CBF / mmHg)[6], which may, in part, be attributed the use of a LL strategy that mitigates the influence of hypercapnia-induced transit time changes[7]. Poor ASL-CVR image quality and presence of negative values may be attributed to degraded ASL SNR in WM[8]. In terms of long-term reproducibility, ASL-CVR was similar to BOLD-CVR based on between-day CVs and these values were superior to a previous report using a 5 % fixed CO_2 gas challenge (CV > 40 %)[9].

References: 1. Mandell DM, *et al.*, Stroke, **39**:2021-8, (2008); 2. Prisman E, *et al.*, JMRI, **27**:185-91, (2008). 3. Slessarev M, *et al.*, J Physiol., **581**:1207-19, (2007); 4. Ito S, *et al.*, J Physiol., **586**:3675-82, (2008); 5. Gunther M, *et al.*, MRM, **46**:974-84 (2001); 6. St. Lawrence K, *et al.*, JMRI, **15**:628-35 (2002). 7. Bolar DS, et al., ISMRM, **716**, (2004). 8. Van Geldern P, *et al.*, MRM, **59** :788-95 (2008). 9. Leontiev O, *et al,*, Neuroimage, **35** :175-84 (2007).

	Baseline ASL CBF (ml/100g/min)			BOLD-CVR (% MR signal /mmHg)			ASL CVR (% CBF / mmHg)		
Region	Trial 1 Mean	Trial 2 Mean	CV (%)	Trial 1 Mean	Trial 2 Mean	CV (%)	Trial 1 Mean	Trial 2 Mean	CV (%)
GM	34.2± 3.8	34.4 ± 5.2	7.9 ± 2.4	0.266 ± 0.032	0.258 ± 0.018	16.5 ± 5.4	7.1 ± 1.0	6.5 ± 0.8	13.9 ± 6.8
WM	25.5 ± 3.3	27.2 ± 3.9	7.1 ± 3.8	0.188 ± 0.022	0.183 ± 0.014	18.4 ± 5.8	6.4 ± 1.0	5.9 ± 0.5	16.3 ± 7.4

Table 1. N = 4. Test-retest baseline CBF, BOLD-CVR and ASL CVR values (mean ± SEM); coefficient of variation (CV), (mean ± SEM);