Repeatability of ASL cerebral blood flow and BOLD cerebrovascular reactivity measurements using a computer-controlled gas delivery system in a pediatric animal model

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Introduction: Cerebrovascular disease is the major cause of stroke leading to mortality or long-term disability in children. A noninvasive means of measuring cerebral blood flow (CBF) reserve would facilitate assessment and clinical management of these patients. Cerebrovascular reactivity (CVR), an indirect measure of CBF reserve, is defined as the CBF response to a vasodilatory stimulus. The BOLD MRI signal has been used as a surrogate for CBF and a change in partial pressure of CO_2 (PCO_2) in blood is typically used as the provocative stimulus. The recent introduction of precise control of end-tidal PCO_2 ($P_{ET}CO_2$) and PO_2 ($P_{ET}O_2$) via a computer-controlled, model-driven prospective end-tidal targeting (MPET) system has improved the reliability of BOLD-based CVR measures in healthy adults[1,2] as well as in adults with cerebrovascular disease[3]. However, MPET is designed for spontaneously breathing subjects, whereas many paediatric patients require general anesthesia and mechanical ventilation to successfully complete an MR scan. The purpose of this study was to adapt MPET to ventilated subjects and test its ability to generate BOLD CVR images in a mechanically ventilated juvenile porcine model. Specifically, we assessed repeatability of BOLD CVR against arterial spin labeling (ASL) measures of CBF at baseline $P_{ET}CO_2$.

Methods: Nine anesthetized, intubated and mechanically ventilated juvenile pigs (10 kg [5.2 – 25.8 kg]) were imaged on a 1.5 T GE Signa MRI scanner. $P_{ET}CO_2$ and $P_{ET}O_2$ targets were achieved using a MPET (RespirAct™, Thornhill Research Inc., Toronto, Canada)[4] with a custom built MRI-compatible secondary circuit designed to provide sequential gas delivery with any standard ventilator (Figure 1). This custom breathing circuit enables a cycle of sequential rebreathing as described by Slessarev *et al.*[4], which maintains $P_{ET}CO_2$ levels in close agreement with arterial blood gases[5].

Repeatability was assessed by collecting consecutive test-retest BOLD-CVR (~ 4 min apart) and consecutive test-retest CBF (~ 2 min apart) data sets. Regional tissue segmentation was performed on a 3D T_1-weighted fast spoiled gradient-recalled echo image volume collected with the following parameters: TE = 4.2 ms, TR = 8.46 ms, flip angle = 20°, FOV = 180 mm, slab thickness = 180 mm, matrix size = 192 × 192 × 120. ASL was performed using the FAIR approach with background suppression and arterial saturation (850 ms post-inversion) using spiral gradient-echo imaging with a 1.7 s label inversion time[6]. For each ASL trial, sixty-four perfusion-weighted (ΔM) signals were acquired at $P_{ET}CO_2$ = 40 mmHg with FOV = 160 mm, matrix size = 64 × 64, slice thickness = 5 mm, slice separation = 1 mm, slices = 6, TE = 4 ms and TR = 3.75 s. Test-retest BOLD-CVR measures were acquired during four iso-oxic square-wave cycles of hypercapnia ($P_{ET}CO_2$ = 55 mmHg for 60 s) and normocapnia ($P_{ET}CO_2$ = 40 mmHg for 60 s). BOLD imaging parameters included: TE = 40 ms, TR = 2 s, FOV = 160 mm, matrix size = 64 × 64, slices = 16, slice thickness = 4.5 mm, volumes = 270 and scan time = 9 min.

The CBF images were generated from average ΔM images using a single compartmental model as previously described[7]. The BOLD-CVR was determined by the slope of the linear regression of the % BOLD signal and $P_{ET}CO_2$ following temporal matching of the $P_{ET}CO_2$ and BOLD MRI time courses. Using the 3D anatomical volumes, we semi-automatically identified cortical grey matter (CGM), cortical white matter (CWM), deep GM (DGM) and deep WM (DWM) regions to extract mean CVR and CBF. Repeatability was quantified using the between-trial intraclass correlation coefficient (ICC) and coefficient of variation (CV).

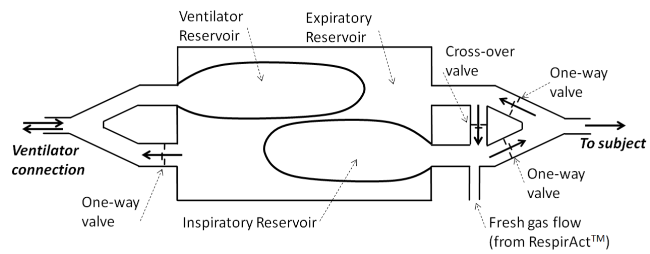

Figure 1. Secondary breathing circuit. The ventilator reservoir inflates during inhalation forcing inspiratory reservoir gases to the subject until exhausted, after which the cross-over valve directs expiratory reservoir gases to the subject.

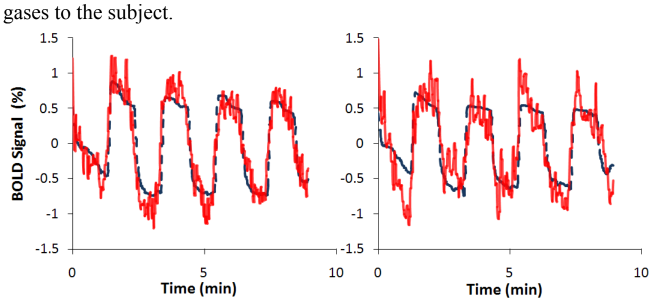

Figure 2. Representative test (left) and retest (right) global BOLD signal (red solid line) with the modeled $P_{ET}CO_2$ (dashed blue line).

Results: Each square-wave $P_{ET}CO_2$ step exhibited excellent test-retest repeatability (CV < 2 %), which generated reliable BOLD single changes that matched the $P_{ET}CO_2$ cycle (Figure 2). The ICC and CV repeatability measures for the BOLD-CVR results for all four regions exhibited excellent BOLD CVR repeatability (ICC > 0.84, Table 1). Regional CBF reliability measures are provided in Table 2. Similar to the BOLD CVR, between-trial ICC and CV results for ASL measures of CBF also exhibited excellent reproducibility for the CGM, CWM and DWM regions (ICC > 0.93); whereas, CBF in the DGM only exhibited fair-to-good repeatability (ICC = 0.60) due to an outlier CBF measurement in the second trial of one animal.

Discussion: In this study, we present the first application of a MPET in anesthetized and mechanically ventilated animals during BOLD-CVR imaging. In the absence of previous literature for comparison, we evaluated BOLD CVR reliability against an established cerebrovascular imaging technique, ASL, which has been validated in newborn pigs[7]. BOLD-CVR repeatability was classified as excellent (ICC > 0.84 for all brain regions), which is similar to the repeatability of ASL baseline CBF measures for most regions. The BOLD-CVR repeatability in the current study (CV < 9 %) was superior to a human study that investigated the short-term BOLD-CVR reproducibility (GM CV = 23.8 % and WM CV = 24.7 %) for a 10 % fixed CO_2 concentration challenge[8]. Improved repeatability of BOLD CVR in the current study is mostly likely attributed to a combination of reduced subject motion (anesthesia) and reliable control of $P_{ET}O_2$ and $P_{ET}CO_2$ transitions. The application of end-tidal gas targeting with MPET to mechanical ventilation will enable further studies of cerebrovascular function in animal models. In addition, translation of this method to clinical pediatric imaging has the potential of adding CVR to the assessment of small children with cerebrovascular disease that require anesthesia for scanning.

References: 1. Prisman E, *et al.*, JMRI, **27**:185-91, (2008); 2. Kassner A, *et al.*, JMRI, *in press*; 3. Mandell DM, *et al.*, Stroke, **39**:2021-8, (2008); 4. Slessarev M, *et al.*, J Physiol., **581**:1207-19, (2007); 5. Ito S, *et al.*, J Physiol., **586**:3675-82, (2008); 6. St. Lawrence K, *et al.*, MRM, **53**,735-8(2005). 7. Koziak AM *et al.*, MRI, **26**:543-53 (2008); 8. Goode SD, *et al.*,AJNR, **30**:972-7 (2009).

	BOLD-CVR (% MR signal /mmHg)				Baseline ASL measures of CBF (ml/100g/min)			
Region	Trial 1 Mean	Trial 2 Mean	CV (%)	ICC	Trial 1 Mean	Trial 2 Mean	CV (%)	ICC
CGM	0.058 ± 0.006	0.060 ± 0.008	6.3 ± 1.5	0.93 [0.75 0.98]	53 ± 4	53 ± 4	1.4 ± 0.7	0.96 [0.84, 0.99]
CWM	0.050 ± 0.005	0.051 ± 0.006	6.6 ± 1.1	0.94 [0.77, 0.99]	41 ± 2	41 ± 2	4.0 ± 2.2	0.60 [-0.26 0.92]
DGM	0.054 ± 0.005	0.052 ± 0.005	7.0 ± 2.1	0.91 [0.67 0.98]	68 ± 3	68 ± 3	2.7 ± 1.1	0.93 [0.69, 0.98]
DWM	0.051 ± 0.004	0.050 ± 0.004	7.8 ± 1.8	0.84 [0.46, 0.96]	55 ± 3	54 ± 3	2.5 ± 1.1	0.96 [0.79 0.99]

Table 1. Mean BOLD-CVR (N = 9) and ASL CBF (N =7) values (mean ± SD); CV, (mean ± SD); and, ICC, (mean [95 % confidence interval])