Comparing Cerebrovascular Reactivity Measured using BOLD and Cerebral Blood Flow at Various Vascular Tension Levels

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Target Audience: This works is intended for those interested in measuring cerebrovascular reactivity in health and disease.

Purpose: Cerebrovascular reactivity (CVR) is an important metric of cerebrovascular health. While the BOLD fMRI method in conjunction with carbon-dioxide (CO_2) based vascular manipulation has been the most commonly used, the BOLD signal is not a direct measure of vascular changes, and the use of arterial-spin labeling (ASL) cerebral blood flow (CBF) imaging is increasingly advocated. Nonetheless, given the diverse CO_2 manipulation types currently used in the literature (including mixed-gas hypercapnia [1], breathholding [2], hyperventilation [3] and deep-breathing [4], etc.), knowledge of potential biases introduced by each technique is critical for the interpretation of CVR values. Moreover, understanding the relationship between CVR measurements and vascular tension would help interpret CVR measurements in patients as well as increase CVR data reliability in healthy controls. However, there has yet to be a direct comparison of BOLD- and CBF-based CVR measurements at different levels of vascular tension and using different vascular stimuli.

Methods: This work involves 18 healthy adult volunteers (10 male, age 26.3 ± 6.5 years; range 18 to 36 years). All were imaged on a Siemens TIM Trio 3 Tesla scanner (Siemens, Erlangen, Germany) with 32-channel head coil reception. We obtained simultaneous BOLD-CBF measurements using a dual-echo pseudo-continuous (pCASL) technique, with a TR of 4 s, TE1/TE2 = 10/25 ms, field of view = 220 × 220 mm, 18 slices (ascending interleaved order), voxel size = 3.4×3.4×5.0 mm^3, 100 frames, bandwidth = 2520 Hz/pixel and GRAPPA = 2. The labeling duration was 1500 ms.

All vascular manipulations were achieved using the RespirAct™ system (Thornhill Research, Toronto, Canada). During the pCASL scans, $PETCO_2$ was sinusoidally modulated [5] at each baseline $PETCO_2$ with a period of 120 s; 3 periods of sinusoidal $PETCO_2$ variations were induced, following a 1-minute baseline. We chose such a bipolar paradigm as it includes both vasodilatory and vasoconstrictive components. We further imposed different levels of baseline vascular tension by inducing hypocapnic and hypocapnic baselines (***Figure 1***).

The modulated CBF component, which is less affected by the BOLD-weighted tissue component, was extracted by high-pass filtering the pCASL signal, followed by demodulation [6]. BOLD contamination in the CBF time series was minimized as described in [7]. For each voxel, outlier removal was performed by removing points from the time courses that fulfill Student's criterion or a Cook's distance greater than *4/N,* where *N* is the number of time points. The inter-subject mean CBF-derived and BOLD-derived CVR were regressed for multiple regions of interest. Before regression, outlier were removed based on Student's criterion. In addition, we used multi-variate and univariate ANOVA as well as Student's *t*-test to assess the dependence of CVR and CVR-delay values on the level of vascular tension and the type of vascular stimulus.

Figure 1

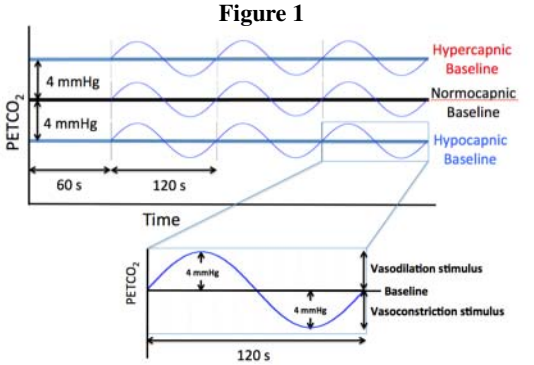
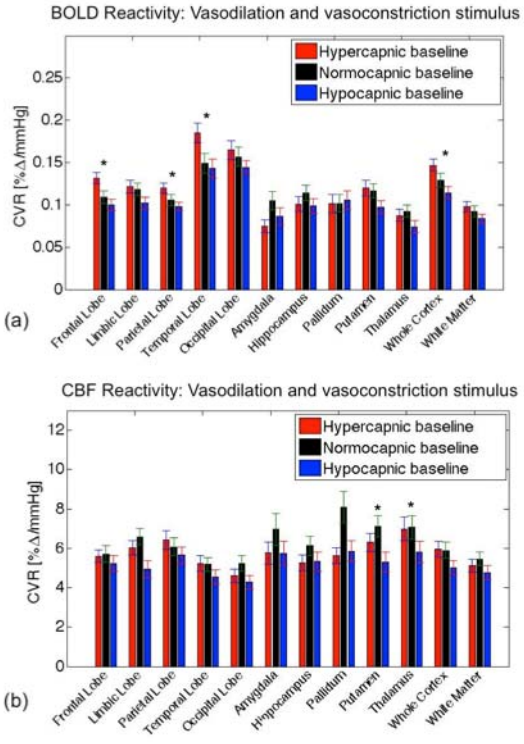


Figure 2



Results: BOLD- and CBF-based CVR measurements were significantly correlated in the majority of brain regions. We saw significant and diverse dependencies on vascular stimulus and baseline condition in both BOLD and CBF CVR measurements: (i) Vasodilatory responses are greater than vasoconstrictive responses for BOLD- and CBF-CVR; (ii) BOLD-based CVR is more sensitive to basal vascular tension than CBF-based CVR (***Figure 2***: asterisk = significant difference between baselines); (iii) the use of a combination of vasodilatory and vasoconstrictive stimuli reduces the vascular-tension dependence of both BOLD- and CBF-CVR.

Discussion and Conclusion: Our finding of higher dilatory than constrictive BOLD and CBF responses is in agreement with previous work [3]. Moreover, as vascular tension can often be altered by potential pathology, our findings are important considerations when interpreting CVR measurements in health and disease. Even within our small range of variations of vascular tension, we saw significant and diverse biases in both BOLD- and CBF-based measurements of CVR. Our finding of lower CBF-CVR dependence (than BOLD CVR) on vascular tension, in general agreement with previous work [8]. This is also the first study to show that a bipolar stimulus is associated with lower CVR-measurement dependence on basal vascular tension compared to hypercapnic or hypocapnic challenges alone. These varying sensitivities of MRI techniques should be considered when designing and interpreting CVR imaging studies.

Reference: [1] Kassner *et al.* J Magn Reson Med 2010; 31: 298-304; [2] Murphy *et al.* NeuroImage 2011; 54: 369-379; [3] Tencredi and Hoge. J Cereb Blood Flow Metab 2013; 33: 1066-1074; [4] Bright *et al.* NeuroImage 2009; 48: 166-175; [5] Blockley *et al.* Magn Reson Med 2011; 65: 1278-1286; [6] Chuang *et al.* NeuroImage 2008; 40: 1595-1605; [7] Tak *et al.* NeuroImage 2014; 84C: 672-680; [8] Ghariq *et al.* ISMRM 2014; 213.