Non-invasive identification of crossed cerebellar diaschisis following cerebral ischemic stroke using combined measures of cerebrovascular reactivity, cerebral blood flow, and Wallerian degeneration

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Target Audience: Researchers interested in practical non-invasive MRI methods to evaluate cross cerebellar diaschisis hemodynamics.

Purpose: Cross cerebellar diaschisis (CCD) is a hypometabolic condition associated with reduced cerebellar blood flow to the hemisphere contralateral to a supratentorial lesion[1]. These effects are thought to result from arterial vasoconstriction, but with preserved cerebrovascular reactivity (CVR) capacity. CCD remains poorly understood partly owing to use of diagnostic modalities not readily available and/or not suitable for longitudinal monitoring, e.g., PET, SPECT, and Gd-MR. Dynamic susceptibility contrast (DSC)-MRI remains the most frequently reported MR metric, but results are mixed, with some reporting lack of sensitivity compared to PET[2]. Non-invasive methods for measurement of cerebral blood flow (CBF), such as arterial spin labeling (ASL), have potential in aiding diagnosis and understanding of CCD. Alternatively, non-invasive hypercapnic BOLD fMRI may be used to assess cerebellar CVR, which should demonstrate asymmetric CVR due to initially reduced CBF in the affected hemisphere. The primary aim of this study was to determine whether reduced cerebellar CVR contralateral to supratentorial infarcts correlates with structural and clinical measures of CCD, including Wallerian degeneration, corticospinal tract infarct, and clinical motor scores of impairment. A supplementary aim was to determine whether non-invasive ASL MRI improved CCD patient discriminability when considered alongside BOLD CVR.

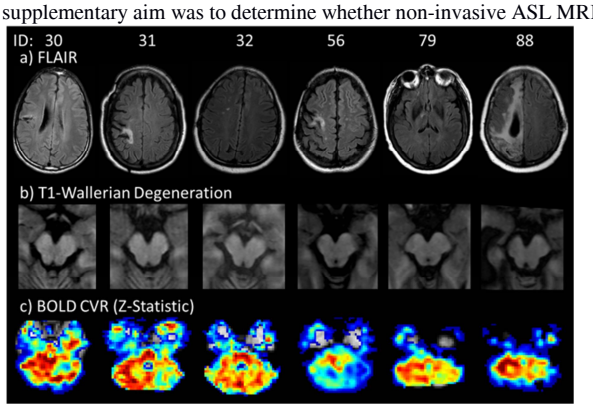

Fig. 1. Representative images from patients with right supratentorial lesions identified as demonstrating structural and clinical indicators of CCD. a) T2-weighted FLAIR images of supratentorial lesions. b) T1-weighted images demonstrating Wallerian degeneration of the cerebellar peduncle. c) BOLD-weighted CVR maps demonstrating reduced CVR in the left (contralateral) cerebellar hemisphere.

Methods: *Experiment.* Patients (n=74) with intracranial vascular disease provided informed, written consent in accordance with local IRB guidelines and were scanned at 3T (Philips). Participants were fitted with a nasal cannula for EtCO2 monitoring and a nonrebreathing facemask for gas administration. To assess CVR, patients underwent a hypercarbic-hyperoxic gas challenge (3 min x 2) while BOLD fMRI data (TR/TE=2000/35ms; spatial resolution=3x3x4 mm^3) were acquired. To assess baseline CBF, pseudocontinuous pCASL (TR/TE=4000/13ms; labeling pulse train=1.6s; post-labeling delay=1.5s; spatial resolution=3x3x7 mm^3) data were acquired. Additional structural data including T_1-weighted MPRAGE imaging (TR/TE=8.9/4.6ms; flip angle=8°; resolution=1 mm^3), FLAIR (TR/TE=11000/120ms; flip angle=90°; resolution=0.9x1.0x5 mm^3), and digital subtraction, computed tomography, or MR angiography (DSA, CTA, MRA) within 30 days of BOLD and pCASL imaging were obtained. *Analysis.* (1) BOLD data were corrected for slice-timing, motion, and baseline drift. Z-statistics (signal change normalized by standard deviation) were then calculated as a surrogate measure of CVR. pCASL data were surround-subtracted, normalized by M_0 to generate CBF-weighted maps and CBF was quantified through application of the solution to the flow-modified Bloch equation[3]. BOLD and CBF data were normalized to 4 mm^3 MNI space. T_1-weighted images were independently scored by two board certified neuroradiologists for Wallerian degeneration. Asymmetry indices were calculated for BOLD CVR, baseline CBF, and Wallerian degeneration. Clinical motor function was assessed by a neurologist who reviewed the emergency medical report.

Results and Discussion: Of 74 patients, 15 had no infarcts (controls; 9F/6M; age=57±12 yrs), 22 had unilateral anterior circulation infarcts (14F/8M; age=49±16 yrs), from which 8 met inclusion criteria (asymmetric CVR and Wallerian degeneration, and no significant vertebro-basilar stenosis) for CCD. **Fig. 1** presents example images of the 6 patients with right hemisphere supratentorial infarcts demonstrating cerebral peduncle Wallerian degeneration and asymmetric BOLD cerebellar CVR. **Fig. 2** presents cortical and cerebellar CVR maps for a representative CCD patient, along with a time-course depicting reduced, but preserved CVR in the cerebellar hemisphere contralateral to the supratentorial infarct. Among all infarct patients, those with CCD demonstrated clear BOLD-CVR (Z-statistic) asymmetry trends, while non-infarct patients demonstrated relative symmetry. Results indicate CCD subjects demonstrated significant cerebellar basal CBF and CVR asymmetry relative to infarct control patients without CCD (P=.006 and P=.002; respectively) and controls (P=.008 and P=.01; respectively); **Fig. 3**. Interaction analysis demonstrated that together, BOLD and CBF asymmetry predicted CCD (P<0.05), however, BOLD asymmetry on its own had greater predictive power (P=0.03). The primary findings from this study are that (i) CCD, as defined by Wallerian degeneration, corticospinal tract infarcts, and impaired motor scores, is significantly associated with reduced cerebellar CVR in the contralateral cerebellar hemisphere and (ii) baseline cerebellar CBF is significantly reduced in the contralateral hemisphere. The stronger, independent predictive power of BOLD CVR suggests this method has potential as an alternative, non-invasive surrogate marker of CCD.

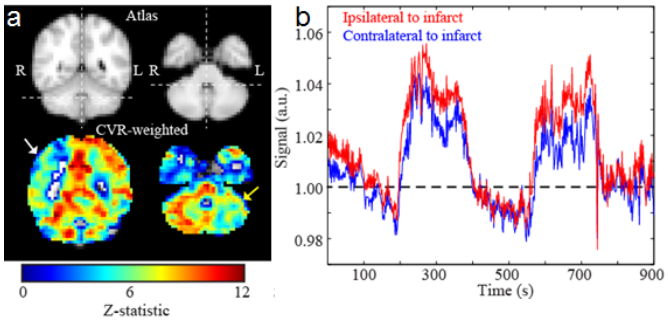

Fig. 2. CVR maps for a representative patient with asymmetric CVR. a) White arrow indicates location of supratentorial infarct (R) and corresponding reduction in CVR, while yellow arrow indicates reduced contralateral (L) cerebellar CVR. b) BOLD time-courses for both cerebellar hemispheres indicating hemisphere contralateral (blue) to supratentorial infarct displays reduced, but preserved CVR relative to the ipsilateral (red) hemisphere.

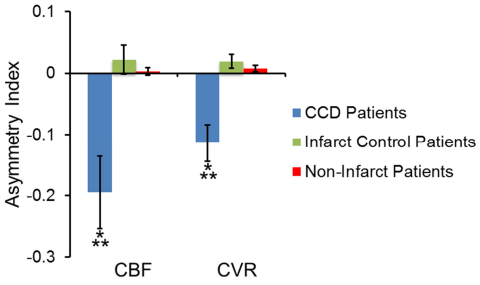

*Fig. 3. Cerebellar CBF and CVR asymmetry indices for non-infarct patients, infarct patients without CCD, and infarct patients with CCD. CCD patients demonstrate clear CBF and CVR asymmetry relative to infarct patients without CCD and non-infarct patients. **=significantly different than infarct control patients; *=significantly different than non-infarct patients.*

Conclusion: Analysis of cerebellar CVR-weighted BOLD data may be a viable, non-invasive alternative to PET, SPECT, and Gd-MR imaging for identifying CCD, as cerebellar CVR correlates with both structural and clinical symptoms of CCD.

References/Funding: [1]Meneghetti,G.*JCBFM*.1984;4:235-240. [2]Madai,VI.*JCBFM*.2011;31:1493-1500.[3]Wang, J.*MRM*.2002;48:242-254.NIH/NINDS 5R01NS078828.