Routine clinical evaluation of cerebrovascular reserve capacity in patients with atherosclerotic and non-atherosclerotic intracranial stenosis using carbogen MRI

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Target Audience: Researchers interested in clinical evaluation of functional imaging methods in ischemic steno-occlusive cerebrovascular disease

Purpose: Patients with intracranial (IC) stenosis have a high (15-20%) two-year stroke incidence, however the correct management (i.e., surgical revascularization vs. aggressive medical management) for these patients is currently unclear[1]. Improving treatment decisions in this high-risk population requires better abilities to monitor progression of hemodynamic compromise over time. Cerebrovascular reactivity (CVR) measurements induced by changes in blood oxygenation secondary to hypercarbic gas administration have great potential in such patients[2]. While such CVR MRI measurements are popular in research settings, two factors have slowed a transition to clinical stroke imaging. First, the safety of hypercarbic gas mixtures is unclear in patients in acute or subacute stages of stroke, as challenging vasculature operating near reserve capacity may exacerbate symptoms or even lead to new events. Second, administration of hypercarbic gas mixtures frequently involves unique setups that utilize mechanisms of end-tidal forcing or similar procedures[3], whereby expired gases are tightly regulated in real time. While tremendously controlled, these systems generally require more time than is possible on a busy clinical radiological unit. Alternatively, carbogen, consisting of hypercarbia with a balance of oxygen (i.e., 5% CO2/95% O_2) can also induce CVR, yet while increasing the fraction of inspired oxygen (FiO_2) and oxygen transport to tissue[4,5]. Therefore, carbogen is potentially a safer hypercarbic gas mixture in patients following stroke. However, carbogen adds complications owing to effects of hyperoxia on metabolism and increases in oxygen saturation, which will cause non-CVR specific increases in arterial and venous blood oxygenation[6]. To better understand carbogen-elicited CVR in stroke, we applied a carbogen MRI protocol in IC stenosis patients using standard gas delivery equipment available at most hospitals. Factors regarding implementation time and expertise, patient compliance, and safety were evaluated, in addition to the utility of the carbogen stimulus for predicting clinical measures of impairment.

Methods: *Volunteer Demographics.* Patients (n=54) with (n=31) and without (n=23; i.e., Moyamoya) atherosclerotic IC stenosis were enrolled for this prospective study. Stenosis degree was classified from angiography performed within 60 days. *Experiment.* Monitored parameters included heart rate, blood pressure, sPO_2, and $EtCO_2$. The stimulus paradigm consisted of two blocks of 3 min carbogen administration (5% CO2/95% O2) interleaved with 3 min of medical grade air (21% / 79% N2). Standard single-shot gradient echo EPI BOLD images (TE=35 ms) were acquired (Tx/Rx=SENSE-8 head coil / quadrature body coil) with in-plane spatial resolution of 3.5 mm x 3.5 mm and whole-brain coverage (approximately 135 mm foot/head coverage). *Analysis.* BOLD signal change and z-statistic in response to carbogen stimulus, as well as modified Suzuki Score (mSS) for Moyamoya patients and lateralizing stenosis percent for atherosclerotic patients were calculated. Signal changes and z-statistics (both normalized by ΔEtCO2) were recorded in 22 basic brain regions for right and left hemispheres: total gray matter, frontal gray matter, parietal gray matter, occipital gray matter, temporal gray matter, total white matter, caudate, cerebellum, insula, putamen, and thalamus. A Student's t-test was applied to assess significance between healthy (IC stenosis < 50%) and diseased (IC stenosis ≥ 50%) hemispheres. For Moyamoya patients, where disease is primarily bilateral, the CVR was plotted against the modified Suzuki Score (mSS), separately for right and left hemispheres, and Pearson's correlation testing was applied. This analysis revealed how lateralizing disease was reflected in the carbogen-induced CVR measures, separately for different post-processing strategies.

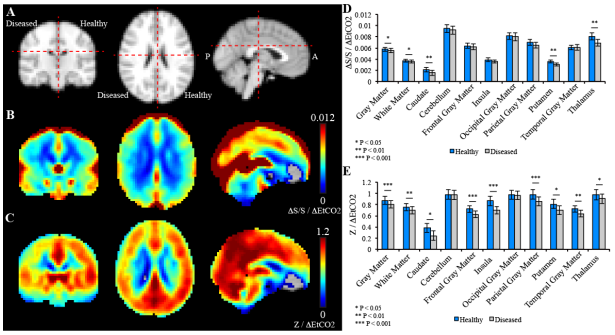

Fig. 1. *(A) Orthogonal slices from the T1-weighted atlas, and corresponding (B) normalized signal changes (ΔS/S0 / ΔEtCO2) and (C) normalized z-statistics (Z / ΔEtCO2). These maps represent group averages from all patients presenting with asymmetric intracranial stenosis (n=33), arranged such that radiological right is diseased and radiological left is healthy. Asymmetric stenosis was defined as one or more MCA segments in one hemisphere with stenosis ≥ 50%, with the contralateral MCA stenosis < 50%. As can be seen, the normalized signal changes (B) show high signal in large vessels owing to the increased sPO2 during carbogen, which is not directly indicative of CVR impairment. However, the normalized z-statistics (C) show much more contrast that is consistent with disease. The (D) normalized signal changes and (E) z-statistics show clear asymmetry in many brain regions, however this significance is generally much higher when normalized z-statistics are considered rather than normalized signal changes. *P<0.05; **P<0.01; ***P<0.001.*

Results and Discussion: No patients exhibited any apparent adverse effects from the short carbogen experiment and all patients completed the experiment. Patients were grouped as to whether they had asymmetric atherosclerotic intracranial stenosis (n=31; age=59±13 yrs; 11/20 F/M) or non-atherosclerotic (Moyamoya) disease (n=23; age=42±13 yrs; 17/6 F/M). **Fig. 1** demonstrates group findings (n=31) in patients with asymmetric atherosclerotic IC stenosis. Clear asymmetry is observed between diseased and healthy hemispheres when z-statistics are considered, which is less apparent when signal changes only are considered (**Fig. 1A-C**) owing to large contributions from draining veins in the signal change maps. This observation is consistent with large intravascular signal in the carbogen-induced signal changes owing to increased HbO_2 in arteries and veins that results from the hyperoxic mixture. Such artifactual CVR reduces when z-statistics are considered, which provide a measure of the signal change normalized by the baseline variability in the signal. The relationship between diseased and healthy hemispheres in the 22 different brain regions demonstrates that asymmetry is apparent in a subgroup of structures when signal changes are considered, whereas contrast between diseased and healthy hemispheres becomes much more apparent when z-statistics are considered. For non-atherosclerotic patients (Moyamoya disease; n=23), disease did not differ significantly (P=0.31; two-tailed paired t-test) between hemispheres (right mSS=2.3±1.3; left mSS=2.6±1.2), as is consistent with the bilateral nature of Moyamoya disease. PCA involvement was also symmetric (P=0.41) albeit with lower disease severity (right PCA stage=1.7±0.9; left PCA stage=1.9±0.8). An inverse correlation (R=-0.51; P<0.001) between parietal carbogen-induced CVR and mSS is observed; no relationship is observed when occipital lobe and PCA staging are considered, owing to lesser PCA territory involvement in these patients. Results demonstrate that in Moyamoya patients, CVR response to carbogen, measured using normalized BOLD z-statistics, inversely correlates with lateralizing disease severity derived from standard angiographic measures and clinical scores. However, quantitative interpretation of absolute signal changes is substantially altered by increases in blood [HbO_2].

Conclusion: Carbogen-induced measures of CVR are potentially safer than CVR measures elicited by other hypercarbic gas mixtures owing to abilities of carbogen to increase oxygen delivery to tissue. Findings demonstrate focal regions of carbogen-induced CVR discrepancy between healthy and diseased hemispheres in intracranial stenosis patients, consistent with angiographic measures of impairment only when z-statistic markers of CVR are utilized. Therefore, vascular stimulation elicited by carbogen inhalation may be a useful method for qualitative CVR assessment when appropriate post-processing steps are taken.

References: 1. Derdeyn CP, et al. *Lancet.* 2013 Oct 25. **2.** Christen T, et al. *AJNR.* 2013 Jun;34:1113-23. **3.** Wise RG, et al. *JCBFM.* 2007 Aug;27:1521-32. **4.** Donahue MJ, et al. *JMRI.* 2013 Nov;38:1129-39. **5.** Ashkanian M, et al. *Brain Res.* 2009 Dec;22:90-5. **6.** Hare HV, et al. *JCBFM* 2013.