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 unclear2. 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 patients2. 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 procedures2, 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% O2) can also induce CVR, yet while increasing the fraction of inspired oxygen (FiO2) and oxygen transport to tissue4,5. Therefore, carbogen is potentially more feasible for use in clinical stroke imaging. The added potential of 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 oxygenation6. 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, sPO2, and EtCO2. 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=xSENSE-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 changes and Z-statistics in response to carbogen stimulus, as well as modified Suzuki Score (mSS) for Moyamoya patients and lateralizing stenoses 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 z-test was plotted against the modified Suzuki Stroke Score (mSS) for Moyamoya patients and lateralizing stenoses percent for atherosclerotic patients were calculated. Signal changes and 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 intracerebral veins in the carbogen-induced signal changes owing to increased HbO2 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 [HbO2].

Conclusion: Carbogen-increased measurements of CVR are potentially safer than CVR measurements 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 qualitative CVR assessment when particular post-processing steps are taken.