Multi-modal Hemodynamic MRI for Evaluation of Tissue Impairment in Patients with Intra-cranial Stenosis

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Introduction. The overall aim of this work is to develop and clinically implement a multi-modal 3.0T MRI protocol capable of quantitatively evaluating the relationship between tissue-level hemodynamic compensation mechanisms and stroke risk in patients with intracranial (IC) steno-occlusive disease. Recent studies have shown high ischemic stroke rates in patients with IC arterial stenosis (1); in such patients with compromised cerebral perfusion pressure (CPP), the extent of hemodynamic compromise reflects the autoregulatory capacity of vasculature to increase cerebral blood volume (CBV) and/or develop collaterals to supplement cerebral blood flow (CBF) (2). The prevalence of CBF collateralization and CBV autoregulation, as well as changes in CBF and CBV in response to stimuli, or cerebrovascular reactivity (CVR), have been hypothesized to correlate uniquely with stroke risk; however, the extent of this correlation has been debated (3, 4). Importantly, new, noninvasive MRI techniques and analysis strategies for assessing hemodynamic impairment have been proposed, yet uncertainties in clinical interpretation and a lack of cross-modal validation studies have precluded routine clinical implementation. We evaluated IC stenosis patients with varying degrees of cerebrovascular disease with the following aims: (i) To compare temporal features (e.g. time-to-peak, TTP) of CVR using controlled, noninvasive hypercapnic BOLD fMRI with standard digital subtraction angiography (DSA) metrics, (ii) to evaluate the relationship between CBF-weighted arterial spin labeling (ASL) MRI, CVR, DSA and Modified Suzuki Score (MSS), and (iii) to assess the utility of CVR and CBF for post-operative evaluation. The fundamental hypothesis to be investigated was that CVR and CBF provide complementary information to DSA opacification times, yet with additional anatomic information. A secondary hypothesis was that a multi-modal structural and functional MRI protocol can be used to assess tissue level hemodynamics following revascularization procedures. Results emphasize the overall utility of noninvasive MRI approaches for evaluating tissue-level impairment in cerebrovascular disease and validate the contrast of these approaches against angiographic and clinical scores.

Methods. *Experiment.* Patients with angiographically-confirmed IC stenosis with (n=15) and without (n=6) Moyamoya disease provided informed, written consent and were scanned using (i) DSA, (ii) T_1-weighted MRI (MPRAGE: 1x1x1 mm^3; TR/TE=8.9/4.6 ms), T_2-weighted FLAIR MRI (0.9x0.9x1 mm^3; TR/TE=11000/120 ms), (iii) CBF-weighted pseudo-continuous ASL MRI (pCASL; 3.4x3.4x5 mm^3; TR/TE/TI=4000/17/1650 ms; 16 slices) and (iv) hypercapnic BOLD MRI (3.4x3.4x5 mm^3; TR/TE=2000/35 ms; 30 slices). All MRI scanning occurred at 3.0T (Philips) using body coil transmission and 8-channel reception. Patients presented with various stages of disease, however a subgroup of patients underwent either direct or indirect revascularization and were scanned pre- and post-intervention. For BOLD CVR, a block paradigm of 3/3 min baseline/5% carbogen repeated twice was used. *Analysis.* In Moyamoya patients, opacification time and MSS were quantified from DSA images separately in right and left middle cerebral artery (MCA) territories by the overseeing neuroradiologist. All MRI data were corrected for motion, baseline drift and were co-registered to T_1 and standard space (MNI; 2 mm). CBF and CVR were quantified in right and left MCA territories. Z-statistics (e.g. statistical strength of change with stimulus) and mean CVR and TTP were quantified as the signal of the final one minute of carbogen breathing relative to baseline normalized by $EtCO_2$ change and time to maximum CVR response, respectively.

Results and Discussion. Adequate co-registration was achieved in 18/21 patients; infarcts in the remaining three patients prevented co-registration and these patients were excluded from group analyses. **FIG 1**. MRI and DSA data from an example IC stenosis patient (51 yr/M) with right MCA stroke. Temporal dynamics of the BOLD timecourse (e) reveal periods of high CVR with short TTP (blue), high CVR with delayed TTP (red), and negative CVR (green); ROIs shown in (**FIG 1c**). Evaluation of these temporal features was a key aim of this work. (f) DSA following right CCA injection reveals chronic right cervical ICA occlusion with ECA collaterals on delayed imaging, yet provides no information of tissue-level hemodynamic compromise. **FIG 2.** Co-registered BOLD CVR maps oriented such that the high (abnormal) MSS hemisphere (2.5+/-1.4) is shown on radiological right, whereas the low MSS hemisphere (1.6+/-1.4) is radiological left. The mean z-maps demonstrate that CVR is approximately twice as high in the low MSS hemisphere, implying that regions with less advanced stages of Moyamoya disease by angiography have improved CVR. BOLD CVR (R=-0.51; P=0.01) and to a lesser degree baseline CBF (R=-0.4; P=0.05) inversely correlated with MSS, whereas no correlation was found between CVR and baseline CBF on average (R=-0.13; P=0.54). **FIG 3.** (a) An inverse relationship is observed between baseline CBF and DSA opacification time (P=0.01), whereas (b) a positive correlation is found between BOLD CVR TTP and DSA opacification time (P=0.04). *These findings provide evidence for BOLD CVR timecourse dynamics providing complementary, yet noninvasive, information to angiography.* **FIG 4.** A patient (28 yr/F) with bilateral Moyamoya disease including left ICA occlusion who underwent indirect revascularization with encephaloduroarteriosynangiosis (EDAS). BOLD CVR six months post-op (b) shows increased local reactivity correlating with the EDAS anastomosis overlying the right frontal cortex. Generally impaired reactivity in the contralateral hemisphere remained constant on both studies with limited, local improvement in reserve only. The noninvasive nature of pCASL and BOLD should enable such patients to be tracked longitudinally to follow revascularization response, which can be extremely varied following surgical revascularization. This information may ultimately predict stroke risk or help stratify patients for additional treatment, when available. The primary finding of this study is that the temporal features of the CVR response correlate with DSA opacification times in right and left ICA territories. Importantly, TTP is delayed in Moyamoya patients (TTP=90+/-27s; n=15), therefore hypercapnic stimulus duration >2 min are likely required. Second, we observed in all but three patients, co-registration of CVR and CBF maps could be performed to high-resolution structural data and standard space atlases, allowing for a regional, tissue-level hemodynamic signature before and after surgical procedures to be assessed with high precision (e.g. **FIG 4**). As all MRI approaches employed here do not require exogenous contrast, this protocol could additionally be used to track impairment and improvement longitudinally, an ongoing aim in our institute.

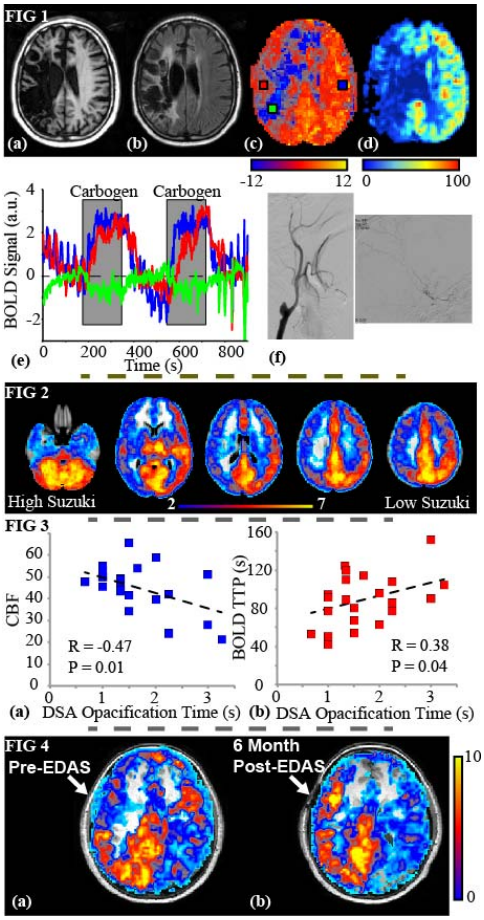

FIG 1. *(a) T_1, (b) FLAIR, (c) BOLD CVR (z-scores) and (d) ASL (CBF; ml/100g/min) for an IC stenosis patient (51 yr/M), with corresponding (e) CVR timecourse and (f) DSA following right CCA injection.* ***FIG 2.*** *Lower MSS corresponds (P<0.05) with higher BOLD CVR (z-score; n=15).* ***FIG 3.*** *Correspondence between (a) baseline CBF (ml/100g/min) and (b) BOLD CVR TTP with DSA opacification time.* ***FIG 4.*** *A patient (28 yr/F) with improved local BOLD CVR (z-score) 6 months post-EDAS.*

References. [1] Ovbiagele B et al. *Arch Neurol*. 2008;65. [2] Hendrikse J et al. *Stroke*. 2004;35. [3] Heyn C et al. *AJNR*. 2010;31. [4] Derdeyn C et al. *Brain*. 2002;125.