Title: Characterizing Hemodynamic Compensation Mechanisms in Patients with Intracranial Stenosis

Summary: The overall aim of this work is to assess the relationship between stroke risk and hemodynamic compensation strategies, as measured using a novel 3.0 Tesla (T) MRI protocol, in patients with symptomatic intracranial (IC) steno-occlusive disease.

Trial Information: Recent studies have shown high two-year ischemic stroke rates of approximately 20% in symptomatic IC stenosis patients. Aggressive therapy for such patients includes revascularization with angioplasty, IC stenting, or bypass, however identification of patients most likely to benefit from these more aggressive interventions, rather than medical management alone, has been problematic. Accurate measurements of hemodynamic compromise are likely required to better define stroke risk and titrate treatment decisions. Specifically, in patients with compromised cerebral perfusion pressure (CPP), the extent of hemodynamic compromise reflects the autoregulatory capacity of vasculature to increase arterial cerebral blood volume (aCBV) and/or develop collaterals to supplement cerebral blood flow (CBF). The prevalence of CBF collateralization and aCBV autoregulation has been hypothesized to correlate uniquely with stroke risk, however the extent of this correlation is debated.

The critical barrier to stratifying stroke risk rests with a lack of (i) methodology for measuring multiple hemodynamic factors with high specificity and (ii) noninvasive approaches capable of monitoring longitudinal progression of impairment. We have demonstrated the clinical utility of relatively new, noninvasive MRI approaches for assessing cerebrovascular reactivity (CVR), aCBV, and collateral CBF. These approaches have been optimized and feasibility assessed in healthy volunteers or isolated clinical studies, however comparatively little information is available regarding the relationship between these collective measures and stroke risk. Therefore, we propose to complement established vascular and structural imaging with more novel, validated hemodynamic measurements to assess complex tissue-level impairment and compensation strategies in patients with IC stenosis. Using a collective approach combining measurements of collateral CBF, aCBV and CVR in multiple brain regions, in conjunction with a statistical model incorporating the above parameters as possible prognostic factors, we will quantify the extent to which two-year stroke risk is associated with hemodynamic compensation mechanisms in a population of symptomatic IC stenosis patients. The noninvasive and multi-faceted scope of this investigation is intended to expand the diagnostic stroke infrastructure and elucidate new hemodynamic prognostic indicators of stroke in this high-risk population.

Hypothesis (1). Perfusion territories that change in response to vascular stimulation are indicative of parenchyma operating near the cerebrovascular reserve, an indicator of stroke risk.

Aim (1). By separately magnetically labeling blood water in different feeding arteries, we will use a tested vessel-selective arterial spin labeling (VS-ASL) approach and a calculated perfusion asymmetry index to noninvasively assess changes in collateral CBF patterns in patients with IC stenosis. IC stenosis patients will be monitored for two years during which their known stroke incidence is 20%. Stroke incidence will be recorded and hypothesized correlations between perfusion asymmetry and stroke risk will be assessed.

Hypothesis (2). Regionally reduced CVR, indicative of vascular steal phenomena, and elevated aCBV, indicative of autoregulatory vasodilation, will positively correlate with two-year stroke incidence.

Aim (2). CVR, as measured using the blood oxygenation level-dependent (BOLD) MRI signal change in response to hypercarbia, will be used to assess cerebrovascular reserve. The inflow vascular-space-occupancy with dynamic subtraction (iVASO-DS) approach, which we have developed and demonstrated in patients, will be applied to assess baseline aCBV. For the same patients in Aim (1), CVR dynamics and aCBV will be assessed for correlations with two-year stroke incidence and collateral CBF.

Hypothesis (3). Collateral CBF, autoregulatory aCBV, and CVR will correlate unequally with two-year stroke incidence, the extent of which can be quantified using a multi-component prediction model.

Aim (3). We will build a statistical prediction model, using collateral CBF, aCBV and CVR as prognostic factors, to quantify the extent to which relationships between the above parameters collectively contribute to stroke risk. The high two-year stroke rate (20%), and large number of admitted patients with symptomatic IC stenosis, will enable this study to detect hypothesized group differences with sufficient statistical power.

This work is a translational extension of optimization work whereby a novel, compensatory hemodynamic protocol is applied to a specific clinical population to understand prognostic potential. Successful completion
should provide new physiological information on tissue hemodynamics and stroke risk in patients that may be used to guide treatment decisions, with the goal of reducing stroke incidence in this high-risk population.