The vascular steal phenomenon is an incomplete contributor to negative cerebrovascular reactivity in patients with symptomatic intracranial stenosis

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Target Audience: Researchers interested in the physiological mechanisms of fMRI signal origins in healthy and ischemic cerebrovascular disease.

Purpose: The overall goal of this work is to apply simultaneous hypercarbia-induced measurements of cerebral blood flow (CBF) and blood oxygenation level-dependent (BOLD) cerebrovascular reactivity (CVR) in patients with symptomatic intracranial stenosis to better understand the physiological origins of negative BOLD CVR. Magnetic resonance imaging (MRI) protocols that exploit the BOLD contrast are capable of measuring CVR in response to a global vasodilatory hypercarbic gas stimulus [1-3], and these approaches are now being used with increased frequency in cerebrovascular disease, dementia, and tumor applications. However, fundamental gaps remain in our knowledge regarding the physiological underpinnings of the BOLD contrast mechanism, and importantly how the BOLD contrast in patients with intracranial vessel disease correlates with prognosis. As such, careful measurements of the BOLD contrast in a clinical setting, together with corroborating data from separate modalities, is required before such imaging protocols can be incorporated routinely into the radiological infrastructure. In healthy tissue, positive BOLD responses arise from increases in blood oxygenation as a result of larger increases in CBF relative to cerebral metabolic rate of oxygen consumption ($CMRO_2$). As hypercarbic stimuli are primarily isometabolic for short stimulus durations (≤3 min) [4,5], BOLD signal increases in healthy tissue are largely driven by CBF. More rarely, negative hypercarbia-induced BOLD responses have been reported in patients with cerebrovascular disease; these negative responses provide support for, but do not confirm, the presence of "vascular intracerebral steal" phenomena whereby blood is re-routed from ischemic parenchyma to healthy parenchyma [6]. Here, independent measures of changes in CBF and BOLD MRI in response to a vascular stimulus in patients with ischemic cerebrovascular disease are recorded to better understand the physiological origins of apparent vascular steal.

Methods: Symptomatic intracranial stenosis participants (n=40) and healthy control volunteers (n=8) provided informed, written consent in accordance with local IRB and HIPAA guidelines and underwent a multimodal 3.0T MRI protocol including structural (T_1-weighted and T_2-weighted fluid attenuated inversion recovery, FLAIR) and hemodynamic (BOLD; TE=35 ms; in-plane spatial resolution=3x3 mm) and CBF-weighted (pCASL; TR/TE=4000/17 ms; in-plane spatial resolution=3x3 mm) functional MRI during room air and hypercarbic hyperoxia (carbogen; 5% CO_2 / 95% O_2) gas administration (3min x 2). Carbogen was used as many patients were in subacute phases of stroke, and it was not appropriate to reduce FIO_2 through hypercarbic or hypoxic gas stimuli. Ramifications of carbogen administration are discussed below. CBF was quantified, upon administration of the flow-modified Bloch equation (including a 200 ms reduction in blood water T_1 upon carbogen administration), in regions demonstrating negative BOLD reactivity. Clinical correlates including degree of arterial stenosis (quantified from digital subtraction angiography and/or CT angiography), as well as symptomatic hemisphere by infarct and lateralizing clinical symptoms were also recorded.

Results: Fifteen of 40 participants exhibited negative BOLD reactivity. Of these, three participants exhibited significant (P<0.01) reductions in CBF with hypercarbia consistent with vascular steal phenomena; six participants exhibited increases (P<0.01) in CBF and the remaining participants exhibited no statistical change in CBF with hypercarbia (Fig. 1). Fig. 2 shows representative examples of two patients exhibiting discrepant changes in CBF despite similar negative BOLD CVR. Secondary findings were that negative BOLD reactivity correlated with symptomatic hemisphere by lateralizing clinical symptoms and prior infarcts(s), and that a strong inverse correlation (P=0.048) exists between the volume of the negative BOLD region and the magnitude of the negative response.

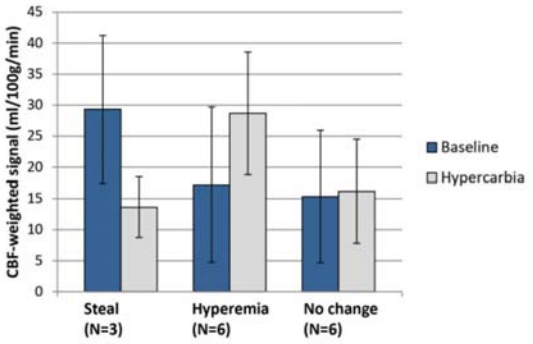

Fig. 1: Baseline and hypercarbia-induced CBF-weighted signal (ml/100g/min) within regions of negative BOLD reactivity, grouped by direction of CBF response.

Discussion: The primary finding of this study is that in patients with symptomatic intracranial steno-occlusive disease, regions of hypercarbia-induced negative BOLD reactivity cannot be exclusively explained by "vascular steal" phenomena. Rather, while a subgroup of such cases does appear to suggest steal phenomena, the majority of participants exhibited no or increased CBF response in these regions. Secondary findings are that negative BOLD reactivity appears most frequently in watershed territories in the symptomatic hemisphere in 30-40% of participants. No control volunteers exhibited negative CVR regions, providing evidence for the variable patient findings being driven by physiology rather than instability in the imaging protocol. Prior experimental and theoretical studies have demonstrated likely roles of elevated CBV secondary to reduced cerebral perfusion pressure [7]. However such auto-regulation is generally believed to occur through the relaxation of smooth muscle surrounding arterioles, rather than from bulk changes in venous CBV. An alternative option that warrants further investigation is that $CMRO_2$ may increase during the hypercarbic hyperoxia stimulus, as hypoxic tissue at baseline may metabolize the additional oxygen provided. This possibility is particularly intriguing, as it suggests that hyperoxia administration may provide a surrogate marker of impaired $CMRO_2$, which is a crucial physiological parameter yet one that has been difficult to measure with MRI approaches.

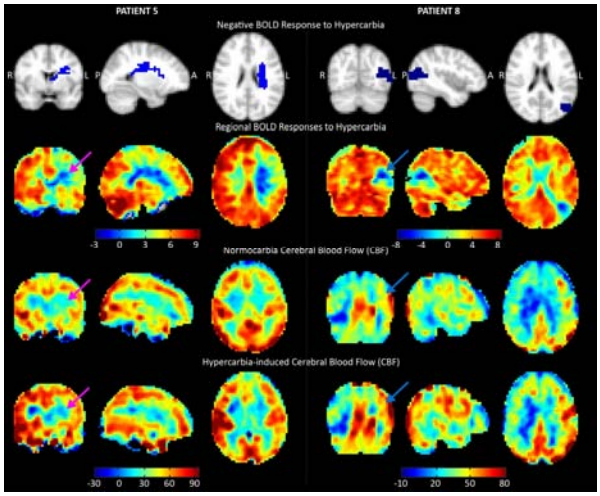

Fig. 2. *Cases of a participant with (Participant 5) and without (Participant 8) apparent vascular intracerebral steal. Orthogonal slices of the negative BOLD CVR regions (blue) are shown at top, followed by BOLD reactivity maps and baseline and hypercarbia-induced CBF maps below. The arrows identify the regions of negative BOLD reactivity.*

Conclusion: The origin of negative BOLD responses in stroke patients is heterogenous, likely containing differential contributions from vascular steal, autoregulation and/or metabolic upregulation.

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