**The promise of non-invasive cerebral hemodynamic assessment in Sickle Cell Anemia**

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Patients with sickle cell anemia (SCA) are at risk of substantial neurological morbidity, including overt stroke, silent cerebral infarction (SCI), and cognitive impairment.1 Monthly transfusions reduce overt stroke risk in children deemed at-risk by presence of SCI2 or transcranial Doppler (TCD) abnormalities, but can lead to burdensome complications, including alloimmunization and iron overload, and may not improve intelligence quotient.2 Abnormal TCD and SCI on MRI are sensitive but not specific screening techniques for stroke risk, and the number needed to prophylactically transfuse to prevent one stroke is as high as 13.2 Many families feel that the risk:benefit is high, and physicians would prefer more precise information to counsel their individual patients. In asymptomatic patients the addition of magnetic resonance angiography (MRA) may improve stroke prediction, but if MR imaging (MRI) is to be undertaken in a young child, it should be optimized to obtain maximum prognostic information.

Even in the absence of radiological abnormality, quantitative MRI studies have revealed widespread and potentially cumulative microstructural injury, with white-matter particularly vulnerable.3 Associated neurocognitive sequelae may affect social and economic mobility, but the mechanisms remain elusive. Reliable methods for assessing risk of SCI, stroke recurrence, microstructural damage, or cognitive impairment, are currently not available.

In this issue of *Neurology*, Fields *et al* employ novel quantitative MRI techniques that enable non-invasive assessment of cerebral hemodynamics in-vivo, including regional brain oxygenation, and provide results that highlight the utility of these techniques in improving understanding of neurological complications in SCA. The authors report higher global cerebral blood flow (CBF), oxygen extraction fraction (OEF), and cerebral metabolic rate of oxygen (CMRO2), in children with SCA compared to their healthy siblings, and identify regions of peak OEF in the deep white matter, that are co-localized with regions of high SCI density, and lower CBF and CMROs.

These results confirm and extend previous reports of potentially reversible mechanisms, related to hypoxic hypoxia as well as anemic hypoxia, that may be investigated to lessen the burden of lower arterial oxygen content (CaO2), the key determinant of CBF,4 in SCA. Compensatory increases in CBF have been widely documented in adults and children with SCA, associated with reduced hemodynamic reserve. This may be documented in individuals using the response to hypercapnia5 and may put children at risk of cerebral ischemia in the setting of seizure or fever requiring increased CBF to match increased metabolic demand. Elevated OEF, but not CBF, is associated with higher levels of clinical impairment in adults with SCA,6 and reliably predicts stroke in adults with carotid disease.7 Field *et al*’s identification of novel, noninvasive imaging biomarkers potentially sensitive to local vascular compromise in children hold promise for identifying those most at risk for future trials of early treatment intervention in SCA.

The data from Fields *et al* are in agreement with the previously described,8 but not well understood, “perfusion paradox” in SCA. Neurologically asymptomatic patients with SCD typically have high *global* CBF but patients with previous or current stroke, stupor, coma, and/or seizures may have decreased CBF and metabolism *globally* or *focally.*9–11 Similar contrasting perfusion profiles, with hyperperfusion in macrocirculatory systems, and hypoperfusion in microcirculatory beds, have been previously reported in renal and forearm studies in SCA.8 Although the mechanisms are unclear, the anatomy of the vasculature may render the deep white-matter particularly vulnerable to vascular instability. Vessels in this region are long, narrow and sparsely distributed, and potentially at risk of occlusion in SCA where increased endothelial adhesion, sludging, and congestion by sickled cells may restrict flow. Regional increases in arterial transit times may also play a role: coupled with the global increases in oxygen demand highlighted by Field *et al*, the heterogeneity of the CBF response to hypoxic exposure,12 and previously reported reduced hemodynamic reserve,5 blood may become partially desaturated before it reaches the deep white matter.

The use of arterial spin labelling for CBF quantification in white-matter requires dedicated sequence optimization, in order to alleviate the intrinsically low signal-to-noise ratio (SNR) and longer arterial transit times in this region. Novel techniques that allow for further modelling of regional hemodynamics, including transit times, may shed further light on vulnerability in this region. Interestingly, although regions of peak OEF overlapped with regions of high SCI density, Field *et al* report few differences in global or segmented CBF, OEF, or CMRO2 between patients with and without SCI, and both patient groups show elevated values compared with controls. Further work is required to investigate the extent to which intracranial and extracranial large vessel disease may play a role in microstructural injury and cognitive impairment, in patients with and without SCI.

This study adds to the literature on novel MRI techniques for improved understanding of pathophysiology in SCA. Measurement using these non-ionizing radiation techniques for local as well as global OEF6 may allow individual prediction of risk, selection of appropriate children with sufficiently high risk for burdensome treatment, and monitoring of therapy so that it is not necessarily lifelong. As with all novel quantitative MRI methods however, the assumptions underlying the calculations need careful consideration: the MR properties of blood, assumed in ASL-based CBF quantification, soon become invalid in persons with reduced hematocrits, and unless these are corrected, CBF will be systematically over-estimated. Assumptions regarding labelling efficiency and arterial transit times, based on a healthy population, will not be directly transferable to patients with altered hemodynamics. A longer post-labelling delay would allow more time for the entire bolus to reach the capillaries in the white matter, and background suppression might improve the signal-to-noise ratio. Validation in adults through comparison with current gold-standard of positron emission tomography will also be required for translation into clinical practice, and MRI sequences need to be shorter so that the cerebrovascular tree can be imaged in the same session as the hemodynamics in an unsedated young child. Some of this work has begun, but much more is needed.

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