Cerebral Blood Flow and Metabolism in Patients with Sickle Cell Disease

Adam Bush[1], Matthew Borzage[1], Thomas Coates[1], and John Wood[1]
[1]*Children's Hospital Los Angeles USC, Los Angeles, California, United States*

Introduction Stroke occurs when cerebral blood flow (CBF) is inadequate to the metabolic needs of the brain. In sickle cell disease (SCD) stroke is common, however accurate quantification of basal cerebral oxygen consumption ($CMRO_2$) is unknown. Early PET studies suggested $CMRO_2$ is decreased in SCD patients [1], but these studies lacked anatomic structural data regarding infarction, brain volume, and relative gray-white matter differentiation; lower $CMRO_2$ may simply have reflected brain loss from prior stroke. Accordingly, we used MRI to measured brain volume, CBF and cerebral venous saturation (S_vO_2) in patients with SCD to address questions regarding cerebral metabolism.

Methods All patients were recruited with informed consent or assent and this study was approved by the Children's Hospital Los Angeles institutional review board. Exclusion criteria included pregnancy, previous stroke, acute chest or pain crisis hospitalization within one month. Fifteen patients with SCD and 12 healthy ethnicity matched controls (CTL) were studied. Arterial oxygen saturation (S_aO_2) was measured via peripheral pulse oximetry. T2 Relaxation Under Spin Tagging (TRUST) was used to measured T2 relaxation of blood within the sagittal sinus [2]; T2 relaxation was converted to S_vO_2 using established calibration curves. OEF represented the difference of S_aO_2 and S_vO_2 divided by S_aO_2. Phase Contrast (PC) of the carotid and vertebral arteries was used to measure global CBF. $CMRO_2$ was calculated as the product of CBF and OEF. T1 weighted images were used for grey-white segmentation and brain volume calculations using BrainSuite® software. Relative grey matter $CMRO_2$ and white matter $CMRO_2$ were estimated by assuming that (gm) $CMRO_2$ was three-fold higher than (wm) $CRMRO_2$. Complete blood count, cell free hemoglobin, LDH, and hemoglobin electrophoresis were measured at the study visit.

Results Table 1 summarizes the results. To compensate for their chronic anemia SCD patients had 167% the CBF of control subjects, producing a normal S_vO_2 and OEF. In fact, oxygen delivery trended higher in patients with SCD than controls leading to higher calculated total $CMRO_2$. $CMRO_2$ increases remained significant even after correction for differences in grey and white matter volumes. We found no correlation between WBC and $CMRO_2$ when tested by population.

Discussion Our study demonstrates elevated cerebral metabolism in SCD, mirroring increases in global resting energy expenditure and peripheral metabolic rate described by others [3,4]. The etiology of the increased $CMRO_2$ is unknown but could reflect neuroinflammation or energy demands from chronic injury/repair. Regardless, our observation at least partially explains the increase of CBF beyond that predicted by anemia alone. By excluding patients with overt stroke and by correcting for differences in brain volume and composition, our data are the first $CMRO_2$ measurements in SCD that are unconfounded by brain volume loss. Given the age differences between our study and control populations, we cannot exclude developmental differences in $CMRO_2$ among patients and controls.

	Controls	SCD	p
Age (years)	37.2 ± 2.8	20.3 ± 2.6	<.05
Sex	9 F, 3 M	9 F, 6 M	ns
Hemoglobin (g/dl)	13.5 ± 1.2	9.6 ± 1.1	<.05
WBC ($10^3/\mu L$)	6.1 ± 2.2	11.0 + 4.2	<.05
$S_a O_2$ (%)	95.7 ± 1.5	94.1 ± 4.1	ns
$S_v O_2$ (%)	65.6 ±6.7	63.6 ± 8.4	ns
OEF	30.0 ± 7.1	32.3 ± 7.4	ns
CBF (ml/100g/min)	70.0 ± 4.6	116.8 ± 19.1	<.05
Cerebral O_2 delivery (µmol O2/100g/min)	193.0 ± 44.9	239.0 ± 35.7	ns
Grey Matter Mass (ml)	499.6 ± 72.0	528.4 ± 58.1	ns
White Matter Mass (ml)	444.6 ± 58.2	422.9 ± 59.5	ns
$CMRO_2$ (µmol O2/100g/min)	193.1 ± 44.9	239.0 ± 35.7	<.05
(gm) $CMRO_2$	250.7 ± 58.7	292.7 ± 39.7	<.05
(wm) $CMRO_2$	175.5 ± 41.1	204.9 ± 27.8	<.05

Table 1: Cerebrovascular flow and metabolism biomarkers in healthy controls compared to patients with SCD.

References:

1. Herold et al. *Stroke*. 1986
2. Lu et al. MRM. 2008
3. Barden et al. JP. 2000
4. Rowly et al. Blood. 2014