Published in final edited form as:

Pediatr Blood Cancer. 2012 November ; 59(5): 773–774. doi:10.1002/pbc.24276.

Anemia, Age, Desaturation and Impaired Neurocognition in Sickle Cell Anemia

Gregory J. Kato, MD [Investigator]

Hematology Branch, National Heart, Lung, and Blood Institute, Bethesda, MD

It is fundamental in the conceptual model of sickle cell disease that rigid red cells resulting from polymerization of sickle hemoglobin inhibit blood flow, resulting in tissue hypoxia and even infarction. However, measurement of tissue oxygen levels has been underinvestigated, particularly in patients. In this issue of *Pediatric Blood & Cancer*, Quinn and Dowling report the results of exploratory description of non-invasive tissue oximetry measurements in children with sickle cell disease at steady state, and relate them to measurements by transcranial Doppler that are accepted surrogate markers for risk of stroke in children with sickle cell disease.

Tissue oximetry measures the oxygen saturation of hemoglobin within the tissue using light in the near infrared spectrum, much as standard pulse oximetry measures oxygen saturation in primarily arterial blood [1]. Near infrared light penetrates tissue more deeply, detecting oxygen saturation in a mixed arterial, venous and capillary bed approximately 1.7 cm deep. The use of near infrared light spectroscopy (NIRS) monitoring of cerebral oxygenation has been growing in the neonatal intensive care unit, cardiac surgery and other critical care settings. The application of tissue oximetry monitoring in sickle cell disease would seem to be a logical application of this new technology. However, only limited results have been published in this area up until now.

In this issue, Quinn and Dowling find that 75% of children with sickle cell anemia have lower cerebral oximetry measurements than the normal reference range. This is consistent with Nahavandi and colleagues at Howard University who used a very early generation NIRS instrument to measure cerebral oxygenation in a pilot study of 27 adults with sickle cell disease compared to controls [2]. Nahavandi found that the mean cerebral oxygen saturation was significantly lower in the group with SS disease compared to 14 healthy and 5 anemic controls (47.7% vs. 61.3% vs. 59.8%, $P < 0.0001$).

Quinn and Dowling link two abnormal physiological measurements together, the cerebral oxygen saturation and the cerebral blood flow velocity, the latter validated as risk predictor of stroke in children with sickle cell disease. Additionally, they show preliminary evidence of asymmetric localization of cerebral hemisphere desaturation to the side detected to have abnormal transcranial Doppler velocity. Does one cause the other? Hypothetically, vasculopathy such as stenosis in the cerebral arteries could lead to decreased regional blood flow and impaired tissue oxygenation, promoting risk of stroke. The converse hypothesis is also tenable based on known autoregulation pathways of cerebral blood flow: Regional brain ischemia due to sickle cell anemia stimulates a compensatory cerebral vasodilatory response that increases blood flow velocity. If this is true, it might help to explain why increased

Corresponding Author: Gregory J. Kato, MD Investigator Hematology Branch, NHLBI National Institutes of Health 9000 Rockville Pike, Bethesda, MD Telephone: (301) 451-8497 Fax: (301) 451-7091 gkato@mail.nih.gov.

Conflicts of interest: None.

cerebral blood flow velocity predicts stroke risk even when associated with increased total cerebral blood flow in the absence of arterial stenoses [3].

What are the causes or consequences of low cerebral oxygen saturation? In a multivariable analysis, Quinn and Dowling find that the independent correlates of cerebral desaturation are anemia, age and pulse oximetry. Each one of these variables merits separate discussion.

Anemia is significantly correlated to low cerebral oxygenation as indicated by NIRS ($\rho = 0.38$, $P < 0.001$). Improvement in anemia by blood transfusion was immediately accompanied by immediate improvement in cerebral oximetry values. This was also reported by Nahavandi, who observed in 7 sickle cell adults that simple transfusion prompted a rise in cerebral oxygen saturation from $32 \pm 2.4\%$ to $45.2 \pm 3.6\%$ ($P < 0.0001$). In their subgroup with limited numbers, the post-transfusion cerebral oxygen saturation correlated very closely with the total hemoglobin level ($r = 0.811$, $P < 0.001$). These consistent findings of lower cerebral oximetry values with more severe anemia in sickle cell disease are reminiscent of recent findings of Vichinsky and colleagues, who show that more severe anemia is associated with worse neurocognitive function in adults with sickle cell anemia [4].

Older age is associated with progressively lower cerebral oxygen saturation among the children screened with NIRS oximetry by Quinn and Dowling (Spearman $\rho = -0.55$, $P < 0.001$). Although correlation to age was not tested by Nahavandi *et al.*, analysis of the raw data provided in their paper on 20 patients in steady state yields remarkably similar correlation in adulthood ($\rho = -0.60$, $P = 0.0048$) [2]. Combined with Vichinsky's observations [4], these three cross-sectional studies imply the grim picture that the most anemic patients with sickle cell anemia generally have cerebral hypoxia and impaired cognitive performance only worsens with age.

The finding of a lower cerebral oxygen saturation as a risk marker by Quinn and Dowling parallels previously published work from Quinn and from several other groups showing in sickle cell patients that low systemic oxygen saturation is a biomarker associated with risks of high cerebral blood flow velocity, cardiopulmonary complications and death [5-8]. Lower saturation detected by these different instruments may be reflecting in part the same biological factors and overlapping clinical risks.

Oxygen saturation is not precisely the same as oxygen concentration, since hemoglobin saturation is a function of not only the partial pressure of oxygen, but also of the oxygen affinity of hemoglobin, which is long known to be low in sickle cells. Sickle erythrocytes have high intracellular concentrations of 2,3-diphosphoglycerate, which decreases oxygen affinity (increased P50), lowering oxygen saturation at any given oxygen tension [9]. Is it possible that lower oxygen saturation in both cerebral and systemic measurements in sickle cell patients is partly a surrogate marker of decreased oxygen affinity of erythrocytes? This is not a trivial matter, because experimentally reduced red cell oxygen affinity in severely anemic mice interferes with microvascular oxygen delivery and extraction even without sickle cell anemia [10]. Furthermore, an increased percentage of deoxyhemoglobin S would be expected to promote sickling and microvascular sludging.

Further research will be required to determine whether low cerebral and systemic oxygen saturation measurements in sickle cell disease directly reflect low oxygen delivery to the brain or alternatively represent an increased pool of deoxyhemoglobin S that increases its polymerization and sickling. Additional investigations with tissue oximetry will contribute to these answers.

Acknowledgments

Dr. Kato receives research funding from the Division of Intramural Research of the National Heart, Lung and Blood Institute at the National Institutes of Health (grant number 1 ZIA HL006014-03 and others).

REFERENCES

1. Drayna PC, Abramo TJ, Estrada C. Near-infrared spectroscopy in the critical setting. *Pediatr Emerg Care*. 2011; 27(5):432–439. quiz 440–432. [PubMed: 21546812]
2. Nahavandi M, Tavakkoli F, Hasan SP, et al. Cerebral oximetry in patients with sickle cell disease. *Eur J Clin Invest*. 2004; 34(2):143–148. [PubMed: 14764078]
3. Prohovnik I, Hurlet-Jensen A, Adams R, et al. Hemodynamic etiology of elevated flow velocity and stroke in sickle-cell disease. *J Cereb Blood Flow Metab*. 2009; 29(4):803–810. [PubMed: 19209182]
4. Vichinsky EP, Neumayr LD, Gold JI, et al. Neuropsychological dysfunction and neuroimaging abnormalities in neurologically intact adults with sickle cell anemia. *JAMA*. 2010; 303(18):1823–1831. [PubMed: 20460621]
5. Johnson MC, Kirkham FJ, Redline S, et al. Left ventricular hypertrophy and diastolic dysfunction in children with sickle cell disease are related to asleep and waking oxygen desaturation. *Blood*. 2010; 116(1):16–21. [PubMed: 20378754]
6. Campbell A, Minniti CP, Nouraie M, et al. Prospective evaluation of haemoglobin oxygen saturation at rest and after exercise in paediatric sickle cell disease patients. *Br J Haematol*. 2009; 147(3):352–359. [PubMed: 19694721]
7. Quinn CT, Variste J, Dowling MM. Haemoglobin oxygen saturation is a determinant of cerebral artery blood flow velocity in children with sickle cell anaemia. *Br J Haematol*. 2009; 145(4):500–505. [PubMed: 19344400]
8. Makani J, Kirkham FJ, Komba A, et al. Risk factors for high cerebral blood flow velocity and death in Kenyan children with Sickle Cell Anaemia: role of haemoglobin oxygen saturation and febrile illness. *Br J Haematol*. 2009; 145(4):529–532. [PubMed: 19344425]
9. Charache S, Grisolia S, Fiedler AJ, et al. Effect of 2,3-diphosphoglycerate on oxygen affinity of blood in sickle cell anemia. *J Clin Invest*. 1970; 49(4):806–812. [PubMed: 5443181]
10. Cabrales P, Tsai AG, Intaglietta M. Modulation of perfusion and oxygenation by red blood cell oxygen affinity during acute anemia. *Am J Respir Cell Mol Biol*. 2008; 38(3):354–361. [PubMed: 17884988]