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Commentary

Clinical Implications of the Association of Fetal Hemoglobin with Peripheral Oxygen Saturation in Sickle Cell Disease

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Sickle cell disease (SCD) refers to a variety of disorders, which result from a single point mutation in the sixth codon of the beta globin gene, causing the replacement of glutamic acid with valine. Although the intracellular polymerization of deoxygenated sickle hemoglobin (deoxy-HbS) into long, rigid, and insoluble fibers causes the primary pathophysiology associated with SCD, the clinical manifestations of SCD are thought to occur due to vaso-occlusion with ischemia-reperfusion injury and hemolytic anemia. SCD affects millions of individuals worldwide, with the majority of patients resident in low resource settings (Piel et al., 2013). Despite the variability in clinical presentation among patients, this chronic disorder impacts nearly every organ, and remains a major cause of morbidity, mortality and healthcare disparities among the affected individuals, while placing an enormous burden on family, caregivers, healthcare providers, and society in general. The severity of SCD may be modified by genetic and environmental factors. The best established genetic modifiers of disease severity are the levels of fetal hemoglobin (HbF) and the presence of concomitant alpha thalassemia (Embury et al., 1982). More recently, genome-wide association studies have shown associations between genetic variants of the inducible form of heme oxygenase-1 and APOL1 G1/G2 with acute chest syndrome (Bean et al., 2012) and chronic kidney disease (Saraf et al., 2015), respectively. Strategies to induce γ-globin expression to increase HbF, which is known to directly inhibit Hb S polymerization, constitute the most successful pharmacological approach to date. Hydroxyurea, a potent inducer of HbF, is known to decrease the frequency of pain crises, acute chest syndrome, hospitalization rates and the need for red blood cell transfusions in both adults and children with SCD (Charache et al., 1995; Wang et al., 2011). However, some evidence suggests that additional mechanisms of action of HbF exist—beyond inhibition of HbS polymerization—and therefore remain key topics of investigation and continued interest in the field.

The current report by Nkya et al. (Nkya et al., 2017) shows associations between HbF, hemoglobin, pulse rate and systolic blood pressure with peripheral oxygen saturation in a large cohort of patients with SCD in Tanzania. The key finding from this study was a strong correlation between peripheral oxygen saturation and HbF levels, despite the overall low levels of HbF in this population. In addition, decreased reticulocyte count was associated with oxygen saturation. The findings from the current study concur with those from a previous, smaller study of Jamaican SS and SC subjects, which showed an association between HbF and peripheral oxygen saturation (reviewed in the current manuscript). The association of HbF with oxygen saturation raises the possibility that therapeutic interventions, which increase the levels of HbF, or increase hemoglobin-oxygen affinity may be clinically beneficial in SCD-related complications associated with hypoxia. Improvement in oxygen saturation has been reported in SCD patients with chronic hypoxemia who were on hydroxyurea therapy (Pashankar et al., 2015). Furthermore, treatment with hydroxyurea was reported to decrease the estimated pulmonary artery systolic pressures of 5 patients with SCD, in association with increased levels of HbF and decreased markers of hemolysis (Olnes et al., 2009). However, the oxygen saturations of the patients in this case series were not reported. Although maximization of hydroxyurea therapy in patients with elevated tricuspid regurgitant jet velocities and pulmonary hypertension has been suggested (Klings et al., 2014), there are no controlled studies that show benefit to such an approach. By increasing oxygen affinity and hemoglobin levels with subsequent increase in oxygen carrying capacity, it is tempting to speculate that increasing levels of HbF may provide benefit to patients with cardiopulmonary disorders associated with hypoxia.

In summary, we anticipate that the current study will stimulate discussions on the potential values and inherent challenges of investigating SCD pathophysiology in similar populations—in this case a population that is hydroxyurea-naïve—with low HbF levels. Additionally, while they do not affect levels of HbF, drugs that increase hemoglobin-oxygen affinity may also prove to be of benefit in the treatment of hypoxic complications associated with SCD. However, adequately controlled studies are required to evaluate these therapies in the appropriate clinical settings.

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Disclosure

Authors declare no conflicts of interest.

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