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Research Paper

Fetal Hemoglobin is Associated with Peripheral Oxygen Saturation in Sickle Cell Disease in Tanzania

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A B S T R A C T

Fetal hemoglobin (HbF) and peripheral hemoglobin oxygen saturation (SpO2) both predict clinical severity in sickle cell disease (SCD), while reticulocytosis is associated with vasculopathy, but there are few data on mechanisms. HbF, SpO2 and routine clinical and laboratory measures were available in a Tanzanian cohort of 1175 SCD individuals aged ≥5 years and the association with SpO2 (as response variable transformed to a Poisson distribution) was assessed by negative binomial model with age and sex as covariates. Increase in HbF was associated with increased SpO2 (rate ratio, RR = 1.19; 95% confidence intervals [CI] 1.04, 1.37 per natural log unit of HbF; p = 0.0004). In univariable analysis, SpO2 was inversely associated with age, reticulocyte count, and log (total bilirubin) and directly with pulse, SBP, hemoglobin, and log(HbF). In multivariable regression log(HbF) (RR 1.191; 95%CI 1.04, 1.37; p = 0.013), pulse (RR 1.01; 95%CI 1.00, 1.01; p = 0.026), SBP (RR 1.008; 95%CI 1.00, 1.02; p = 0.014), and hemoglobin (1.120; 95%CI 1.05, 1.19; p = 0.001) were positively and independently associated with SpO2 while reticulocyte count (RR 0.985; 95%CI 0.97, 0.99; p = 0.019) was inversely independently associated with SpO2. In SCD, improving SpO2, in part through cardiovascular compensation and associated with reduced reticulocytosis, may be a mechanism by which HbF reduces disease severity.

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1. Introduction

Sickle cell disease (SCD) remains the most common hemoglobinopathy worldwide. Clinically, there is great variability amongst individuals with SCD; predictors of severity include hemoglobin F levels, reticulocytosis and alpha globin gene number. A major factor is the wide variation in the innate ability to synthesize fetal hemoglobin (HbF) beyond early childhood. Individuals with high levels of HbF experience milder forms of the disease with lower morbidity and improved survival. HbF level of 10% and above is believed to reduce the risk of major organ failure such as stroke, while much higher levels (20% and above) may be required to prevent recurrent clinical events such as painful crises and pulmonary disorder (Meier et al., 2017). The mechanisms underlying the reduction in the severity of SCD in people with high HbF are not clear. Therefore, studying the associations of HbF and clinical phenotypes of SCD may provide insights into the underlying mechanisms.

Peripheral hemoglobin oxygen saturation (SpO2), measured non-invasively by pulse oximetry, is related to several disease complications. Lower SpO2 has been associated with anemia (Quinn and Ahmad, 2005), increase in reticulocytes (Quinn and Ahmad, 2005), hemolysis (Campbell et al., 2009) and increased episodes of acute chest syndrome (Rackoff et al., 1993) and appears to predict central nervous system complications (including stroke (Quinn and Sargent, 2008), higher transcranial doppler velocity (Quinn et al., 2009), number of days per year admitted for pain (Hargrave et al., 2003), tricuspid regurgitant jet velocity (TRV) (Minniti et al., 2009) and diastolic dysfunction (Johnson et al., 2010) in SCD.

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Studies in fetuses, children with cyanotic heart disease and adults ascending to high altitude suggest that Hbf synthesis increases in hypoxia (Bard et al., 1994). Furthermore, hemolysis may induce Hbf synthesis further (Desimone et al., 1978). There is limited information on the magnitude and direction of any association between Hbf and SpO2 in patients with SCD not on hydroxyurea, but the available data suggest that, as for neonates (Shiao, 2005), SpO2 is higher in SCD patients with higher Hbf (Homi et al., 1997), (Halphen et al., 2014, Cox et al., 2013). In this report, we describe the association between Hbf and SpO2 in individuals with SCD enrolled in the Muhimbili National Hospital cohort in Tanzania.

2. Materials and Methods

2.1. Study Area and Population

This was a cross sectional study conducted at Muhimbili National Hospital (MNH) in Dar-es-Salaam, Tanzania involving individuals with SCD recruited into the Muhimbili Sickle cohort between March 2004 and December 2013. Recruitment and enrolment of patients and diagnosis of SCD has been previously described (Makani et al., 2011). Informed consent was obtained for each patient upon enrolment. Individuals were identified at pediatric SCD or hematology clinics or during hospitalization and were screened for SCD. A diagnosis of sickle cell anemia (HbSS/HbSβ0) by alkaline hemoglobin electrophoresis (Helena, Sunderland, Tyne & Wear, UK) was confirmed by high performance liquid chromatography (HPLC) (Variant I analyzer, Bio-Rad, Hercules, CA, USA). Ethical approval was granted by the Muhimbili University Research and Publications Committee (MU/RP/AEC/VOLX1/33).

Individuals were selected into this study if they had Hbf values measured at the age of five years or above, since this is the age at which Hbf synthesis stabilises. Data were excluded if the patient was on hydroxyurea therapy.

2.2. Clinical Measures

Daytime SpO2 was determined in clinic when the child was well using a pulse oximeter (Nellcor, Pleasanton, CA, USA). Other clinical information that was collected included pulse rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP).

2.3. Laboratory Measures

Hemoglobin was measured by an automated blood cell analyser (ABX Pentra 60 Analyser, Horiba, Kyoto, Japan) and reticulocytes were counted using the new methylene blue staining method followed by microscopy. Hbf measurements were done by HPLC (Variant I, Biorad, Hercules, CA, USA). Routine biochemical analysis included total bilirubin (Roche Cobas Mira, New York, USA or Abbott Architect, New York, USA).

2.4. Statistical Methods

The SpO2 data were collected as counts, which ranged from 82 to 100%, and could not be transformed into a normal random distribution, and hence a Poisson random distribution was assumed after transformation. To convert the distribution of SpO2 (Fig. 1A) into a Poisson distribution, 100-SpO2 transformation was performed, Fig. 1B. The distributions of Hbf and bilirubin were positively skewed and hence normalized by natural log transformation. The association of clinical and laboratory variables with SpO2 (as response variable) was assessed by negative binomial model with age and sex included as covariates, presenting the results as rate ratio (RR) with 95% confidence intervals. A p-value < 0.05 was considered statistically significant. Variables with significant associations with SpO2 in the univariate analysis were included in the multivariable regression analysis.
HbF, which has a higher affinity for oxygen, results in a higher SpO₂ in neonates (Shiao, 2005). In addition, compounds, including an aromatic aldehyde agent, 5-hydroxymethyl-2-furfural (5-HMF, also known as Aes-103), has been found to increase oxygen affinity of sickle hemoglobin and as a result reducing hypoxia-induced sickling in vitro and protects sickle cell mice from the effects of hypoxia (Safo and Kato, 2014).

Pulse rate, SBP and hemoglobin were also positively associated with SpO₂ in multivariable analysis. The direct association of hemoglobin with SpO₂ has been described previously and hence confirmed in the population that we have studied. The direct association of pulse rate and SBP suggests that one of the mechanisms for maintaining an adequate SpO₂ is cardiovascular compensation. The HbF levels for this population are low compared to other populations with different sickle haplotypes; despite this, an association with SpO₂ was established in the population; future studies should include measurement of indirect bilirubin, as a more specific marker of hemolysis, in all patients.

This study reports the association of HbF with SpO₂two variables with strong clinical significance in individuals with SCD. The underlying mechanism of this association and the optimal range for HbF, measures cardiac function such as blood pressure and pulse, and SpO₂ for good health in SCD needs to be established. This information will aid in the development and improvement of HbF-augmenting agents. The findings from this study may be applied to other SCD populations that may be similar.

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### Conflict of Interest

The authors declare no competing financial or other interests.

### Author Contributions

J. Makani, F.J.K, B.P. M and S.N.M. designed the study. J.Mgaya, collected the data. B.P.M. performed the analysis. S.N.M., J.Makani, B.P.M., S.C., C.R.N. and F.J.K wrote the manuscript and all authors commented on the drafts of the manuscript.

### References


