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Mini-symposium: Controversies in the Evaluation and Treatment of Sickle Cell Lung Disease

Hypoxemia in Sickle Cell Disease: Significance And Management

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EDUCATIONAL AIMS

1) Understand the pathophysiology and clinical implications of hypoxemia in children with sickle cell disease.
2) Understand how to accurately assess hypoxemia and oxyhemoglobin saturation in children with sickle cell disease.
3) Understand the clinical approaches to managing hypoxemia in children with sickle cell disease.

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SUMMARY

Hypoxemia is common in SCD and likely exacerbates SCD vasculopathy. Pulse oximeter correlation with arterial oxygen tension in patients with SCD may at times be poor and arterial blood gas confirmation is required in hypoxic patients. Supplemental oxygen should be administered for the correction of hypoxemia, which if untreated creates a risk of multi-organ failure. Transfusion and hydroxyurea can improve oxygen delivery to tissues and organs. The role of supplemental oxygen therapy in preventing or reversing SCD vasculopathy is controversial. Nitric oxide therapy for VOC pain has not fulfilled promise to date. On the other hand, lung distension (CPAP, incentive spirometry, PEP therapy) are promising treatments requiring further study.

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INTRODUCTION

Sickle cell disease (SCD) is an inherited blood disorder characterized by adherent, rigid, abnormally shaped erythrocytes that occlude blood vessels and compromise blood and oxygen supply to tissues and organs. "Hypoxemia," due to decreased arterial blood oxygen content, decreased oxygen carrying capacity due to chronic anemia, and oxyhemoglobin desaturation, is a well-documented phenomenon in patients with SCD. Although the etiologies of "tissue hypoxia," in contradistinction to "hypoxemia," in patients with SCD are complex, persistent and intermittent hypoxemia is recognized as a marker and predictor of vaso-occlusive (VOC) pain crises, acute chest syndrome (ACS), pulmonary hypertension, and progressive lung dysfunction. [1–6] At low oxygen tension, there is increased polymerization of sickle hemoglobin (HbS), making the erythrocyte rigid, distorting its shape to the characteristic sickle appearance, and causing structural damage to the cell membrane, all of which impair blood flow through the microvasculature, and lead to tissue and organ ischemia and infarction. Thus, the cycle of hypoxemia and erythrocyte sickling results in known complications of SCD: hemolysis, stroke, VOC pain crises, and ACS, events responsible for the high morbidity and mortality associated with SCD. [4,7] The extent of HbS polymerization is a primary determinant of the severity of SCD and is proportional to the degree and duration of hemoglobin deoxygenation. [8,9] Chronic hypoxic stress in these patients can also result in irreversible remodeling of the vasculature and development of pulmonary hypertension. [8,10] Since hypoxemia is a trigger for the sickling of HbS, the discovery, accurate assessment, and correction of hypoxemia is of major importance in the management of SCD in children. Unfortunately, there is no consensus on the definition or treatment of hypoxemia in patients with SCD, especially children. [11]

SIGNIFICANCE AND PATHOGENESIS OF HYPOXEMIA

Hypoxemia is prevalent in patients with SCD, during steady-state, in the absence of overt cardiopulmonary illness, and during ACS or VOC crises. [12] Previous studies have shown that daytime

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and nighttime oxyhemoglobin saturation measured by pulse oximetry (SpO_2) is lower, on average, among individuals who have homozygous SCD (HbSS) compared with those who have sickle-hemoglobin C disease (HbSC). [5,12,13] The prevalence of hypoxemia in SCD patients during steady-state, defined as transcutaneous SpO_2 less than 96%, has been reported to range between 33% - 44%. [1,13] Rackoff *et al* showed that in their cohort of 86 clinically well children with SCD, all HbSC patients had SpO_2 values that were in the normal range (96% to 100%); however, 44% of HbSS patients had SpO_2 values lower than 96%. In the HbSS group, a history of ACS and age greater than 5 years were associated with lower SpO_2 values. [13] Quinn *et al* reported that a multi-variable model including decreased hemoglobin concentration, increased reticulocyte count, older age, and male gender explained 45% of the variability in steady-state SpO_2. [1]

Oxyhemoglobin desaturations reported in patients with SCD can be attributed to: a low arterial partial pressure of oxygen (PaO_2); the rightward shift of the oxyhemoglobin dissociation curve; hypoventilation due to upper airway obstruction; and elevated levels of dyshemoglobins, carboxyhemoglobin and methemoglobin. [14–16] During ACS, hypoxemia is common, primarily due to ventilation/perfusion mismatch secondary to pneumonia, atelectasis, and in severe episodes, adult respiratory distress syndrome. [9] Rib, sternum, and vertebral infarcts, with associated chest wall and back pain, occur commonly in the setting of painful VOC pain crises and ACS, and result in splinting, hypoventilation, and pleuritis, predisposing patients to atelectasis and hypoxia, with further VOC crises. [17] Recurrent episodes of ACS can lead to lung parenchymal scarring and sickle cell chronic lung disease, which leads to progressive loss of lung function and/or impaired pulmonary growth (Figure 1). [18] Children with SCD who have recurrent ACS episodes have worse pulmonary lung function compared to aged-matched children with SCD who have not experienced ACS episodes. [19]

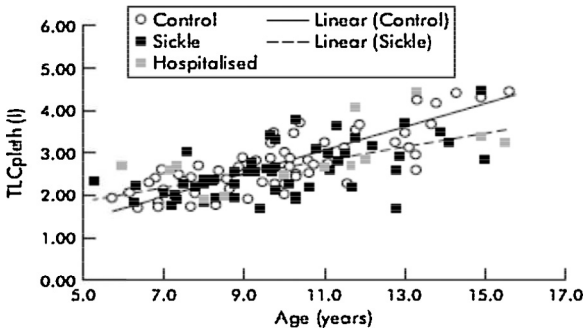

Figure 1. Relationship between age and TLCpleth in children with SCD, children with SCD previously hospitalized, and controls. Regression lines are shown for SCD children (- - -) and controls (—). [18]

Further, steady state daytime and/or nocturnal oxyhemoglobin desaturations are risk factors for overt ischemic stroke in children with SCD. [4,20] Quinn *et al* reported that children with HbSS who develop a stroke have lower pre-stroke daytime SpO_2 values than children with HbSS who do not develop a stroke. [4] A modest decrease in SpO_2 might be physiologically deleterious to a region of the brain that is downstream of a critical stenosis in which oxygen extraction is already maximal.

Hypoxemia and the Respiratory System

Lung Diffusion Abnormalities

Several studies have reported on the carbon monoxide diffusing capacity of the lungs (DLCO) in patients with SCD; results are often contradictory depending on the correction factors used. Most studies report normal or slightly reduced DLCO. [21] Lung volumes tend to be mildly reduced in SCD, [22] and therefore, surface area for diffusion is reduced; if this reduced lung volume is not corrected for, apparent diffusion capacity will be lowered. Likewise, the effects of anemia must be taken into account; the blood component of diffusion is at least as important as the membrane component, and apparent diffusion capacity is reduced in direct proportion to the degree of anemia, if there is not a correction factor for hemoglobin concentration. Some studies have reported a normal or even *increased* DLCO in subjects with SCD, especially in subjects with a history of ACS compared to those without, and have attributed this to an expanded pulmonary capillary blood volume. [23]

Airway Hyperreactivity

Either in the setting of chronic lung disease, or de novo, children with SCD have up to a 77% increased prevalence of airway hyperreactivity, [24,25] and a 20% to 48% increased prevalence of asthma. [26–28] As described by Boyd *et al*., children with SCD who had a clinical diagnosis of asthma had nearly twice as many episodes of ACS (0.39 versus 0.20 events per patient year), had more frequent painful VOC crises (1.39 versus 0.47 events per patient year), and had a more than two-fold higher risk of mortality (hazard ratio 2.36, 95% CI 1.21 to 4.62, $p = 0.01$) when compared to children without asthma, even after controlling for previously identified risk factors (Figure 2). [27,29,30]

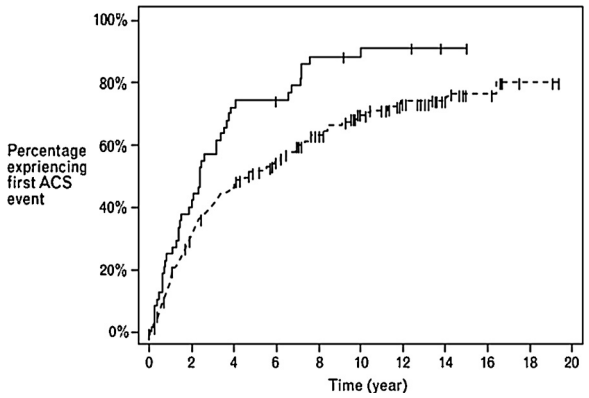

Figure 2. Kaplan-Meier plot of time to first ACS event in a SCD infant cohort. Children with SCD and asthma had nearly twice as many episodes of ACS (0.39 versus 0.20 events per patient year) when compared to children with SCD and no asthma. Asthmatic (- - -); not asthmatic (—). [27]

There are several plausible explanations for the relationship between asthma or airway hyperreactivity in children with SCD and ACS or VOC crises. Based on the pathogenesis of asthma and the relevance of airway obstruction, ventilation-perfusion mismatching may result in tissue hypoxia, promoting increased sickling of erythrocytes, resulting in ACS or VOC pain crises. [27] In addition, the hypoxemia associated with asthma exacerbations could promote sickling in the pulmonary vessels and trigger ACS. [31] Further, inflammatory mediators and oxidant species produced during an asthma exacerbation might increase the expression of endothelial adhesion molecules and adhesion of erythrocytes to the vascular endothelium, resulting in VOC crises. [9]

Pulmonary Hypertension

It is possible to speculate that slowly worsening steady-state oxyhemoglobin desaturation and pulmonary vascular hypoxia could be a marker of developing pulmonary hypertension, which is increasingly recognized as a common and life-threatening complication of young adults with SCD. [1,32] Minniti *et al*