CHEST

Chronic Pulmonary Complications of Sickle Cell Disease

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Sickle cell disease (SCD), the most common genetic hemolytic anemia worldwide, affects 250,000 births annually. In the United States, SCD affects approximately 100,000 individuals, most of African descent. Hemoglobin S (HbS) results from a glutamate-to-valine mutation of the sixth codon of the β-hemoglobin allele; the homozygous genotype (HbSS) is associated with the most prevalent and severe form of the disease. Other SCD genotypes include HbSC, composed of one HbS allele and one HbC (glutamate-to-lysine mutation) allele; and HbS-β-thalassemia^0 or HbS-β-thalassemia$^+$, composed of one HbS allele and one β-thalassemia allele with absent or reduced β-chain production, respectively. Despite advances in care, median survival remains in the fifth decade, due in large part to chronic complications of the disease. Chronic pulmonary complications in SCD are major contributors to this early mortality. Although our understanding of these conditions has improved much over the past 10 to 15 years, there remains no specific treatment for pulmonary complications of SCD. It is unclear whether conventional treatment regimens directed at non-SCD populations have equivalent efficacy in patients with SCD. This represents a critical research need. In this review, the authors review the state-of-the-art understanding of the following pulmonary complications of SCD: (1) pulmonary hypertension; (2) venous thromboembolic disease; (3) sleep-disordered breathing; (4) asthma and recurrent wheezing; and (5) pulmonary function abnormalities. This review highlights the advances as well as the knowledge gaps in this field to update clinicians and other health care providers and to garner research interest from the medical community.

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Sickle cell disease (SCD) is clinically heterogeneous, characterized pathogenically by recurrent episodes of hemolysis and vaso-occlusion. During hypoxia, the hemoglobin (Hb) tetramer (α_2/β_2^S) polymerizes, leading to the classic inflexible crescent shape of the erythrocyte. Hb polymerization and abnormal interactions between erythrocytes and leukocytes, platelets, and the vascular endothelium lead to increased viscosity,

ABBREVIATIONS: ACS = acute chest syndrome; AHI = apnea-hypopnea index; AHR = airway hyperresponsiveness; DLCO = diffusion capacity of the lung for carbon monoxide; Hb = hemoglobin; HbC = hemoglobin C; HbS = hemoglobin S; NT-pro-BNP = N-terminal pro-B-type natriuretic peptide; PAH = pulmonary arterial hypertension; PE = pulmonary embolism; PFT = pulmonary function testing; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RCT = randomized controlled trial; RV = right ventricular; SCD = sickle cell disease; SCD-PH = sickle cell disease-associated pulmonary hypertension; SDB = sleep-disordered breathing; TRV = tricuspid regurgitant jet velocity; VOE = vaso-occlusive event

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impaired microvascular blood flow, tissue ischemia-reperfusion injury, and promotion of inflammation, thrombosis, and oxidant stress.[1]

Despite advances in care, median survival in SCD remains in the fifth decade. Acute and chronic pulmonary complications are among the most common causes of morbidity and mortality, yet our understanding of each of these conditions remains limited. We are focusing the current review on the chronic pulmonary complications of SCD, which affect practically every cell type and structure of the lungs.[2] This is an update for clinicians and researchers to improve the care for these patients and to foster research interests.

Pulmonary Hypertension

Definitions

Pulmonary hypertension (PH), defined hemodynamically as a mean pulmonary arterial pressure ≥ 25 mm Hg at rest, occurs in 6% to 10.4% of adults with SCD.[3-6] Right-sided heart catheterization is the gold standard for the diagnosis of PH[3] and assessment of prognosis. The hemodynamics of PH in patients with SCD are heterogeneous (Table 1). PH may be precapillary (pulmonary arterial hypertension [PAH]), postcapillary (pulmonary venous hypertension), or have features of both.[7] Clinical guidelines from the American Thoracic Society's expert panel define elevated pulmonary vascular resistance (PVR) in patients with SCD as different from other types of precapillary PH because of the anemia-induced elevation of cardiac output, and consequent reduction in PVR that occurs at baseline.[8] In idiopathic PAH, increased PVR is defined as ≥ 240 dynes·s/cm^5 (3 Wood Units), which is 2 standard deviations above the PVR of ≤ 80 to 120 dynes·s/cm^5 (1 Wood Unit) that is observed in healthy volunteers. In adults with SCD, the baseline mean cardiac output is 8 to 9 L/min with a PVR of 0.90 to 0.93 (± 0.31-0.48) Wood Units.[5-7] This suggests that in SCD, ≥ 2 Wood Units is consistent with elevated PVR.[8]

Hemodynamics consistent with precapillary PH occur in approximately 40% to 50% of those with PH and in 2.5% to 5.9% of adults with SCD.[5,7] Although these hemodynamics are typically observed in PAH, in SCD they can also be observed in patients with chronic thromboembolic PH and, at times, in those with an anemia-induced hyperdynamic state. When compared with associated forms of pulmonary arterial hypertension classified as group 1 PAH, this is second only to systemic sclerosis (12%) in terms of frequency.[9] Despite the hemodynamic similarities to group 1 PAH, the most recent PH classification guidelines have placed the PH of SCD into group 5[10] on the basis of (1) features of both precapillary and postcapillary PH[7,11,12] in these patients, (2) a lower PVR compared with group 1 PAH, and (3) coexistent thromboses in some patients similar to group 4 PH.[13] This unfortunately reflects the imprecision of the current PH classification system and stresses the need to better define PH subgroups.[8]

The complex hemodynamics of PH in SCD emphasize the need for right-sided heart catheterization for diagnostic confirmation, and to accurately stratify patients prior to consideration of treatment options. Although the hemodynamics of PH in SCD can differ across patients, all have reduced exercise capacity and survival.[4,14]

Diagnostic Evaluation

In 2014, the American Thoracic Society published evidence-based consensus guidelines for the diagnosis and treatment of sickle cell disease-associated pulmonary hypertension (SCD-PH).[8] The diagnostic evaluation of a patient with suspected PH is similar to that of a patient without SCD (Fig 1).[3]

Patients with SCD and symptoms suggestive of PH should be evaluated initially by echocardiography.[8] Elevated right ventricular (RV) systolic pressure

TABLE 1] Hemodynamic Profiles and Mortality Risk for Pulmonary Hypertension in Sickle Cell Disease

	Precapillary PH	Postcapillary PH	PH with Features of Both Precapillary and Postcapillary PH
mPAP	≥ 25 mm Hg	≥ 25 mm Hg	≥ 25 mm Hg
PAWP or LVEDP	≤ 15 mm Hg	> 15 mm Hg	> 15 mm Hg
PVR	≥ 2 Wood Units	< 2 Wood Units	≥ 2 Wood Units
Survival	Reduced	Reduced	Reduced

LVEDP = left ventricular end-diastolic pressure; mPAP = mean pulmonary arterial pressure; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance.