# Review: Hemodynamic Characteristics and Outcomes of Sickle Cell Disease Associated Pulmonary Hypertension

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Pulmonary hypertension (PH) is a leading cause of morbidity and early mortality in adults with sickle cell disease (SCD). However, the prevalence, hemodynamic profile and prognosis of SCD-PH remain controversial and need frequent updates. Pulmonary hypertension determined by right heart catheterization (RHC) occurs in 6% to 10% of adults with SCD. Hemodynamically, SCD-PH may be pre-capillary or post-capillary in nature. The exact etiology is unknown and often multifactorial; hence a thorough diagnostic evaluation following established PH guidelines is essential to determine disease prevalence, etiology and outcomes. Data on the efficacy and safety of pulmonary arterial hypertension (PAH) therapy are limited in SCD; clinical trials in these patients are urgently needed. This review provides an overview of RHC-determined hemodynamic characteristics, current management modality and outcomes; we also highlight recent advances and unmet research needs in SCD-PH. *Ethn Dis.*2016;26(4):545-552; doi:10.18865/ed.26.4.545.

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## Introduction

Sickle cell disease (SCD) is the most common autosomal recessive genetic disorder worldwide.[1] In the United States, approximately 100,000 individuals are affected by SCD. Most of those affected are of African descent.[2] The term "sickle cell disease" refers to a collection of autosomal recessive genetic disorders characterized by the hemoglobin- S (HbS) variant of the β-globin gene.[3] The most prevalent and severe form of SCD genotype is caused by homozygous presence of hemoglobin S (HbSS). Hemoglobin-S results from the substitution of a valine for glutamic acid at the sixth amino acid of the beta globin chain.[4] Other common compound heterozygote forms include HbSC disease and HbS-beta thalassemia. Hemoglobin SC results from mutations in each of the two β-globin alleles, one HbS and the other HbC (valine-to-lysine substitution). The HbS-b thalassemia$^{+ \text{ or } 0}$ occurs with one HbS and a mutant β-sickle globin with a reduced or absent beta globin expression. Hemodynamic data on SCD-PH comes mainly from SCD adults with the HbSS genotype.

At low oxygen tension, the hemoglobin tetramer ($a_2/b^S_2$) polymerizes into sheets of elongated rope-like fibers, causing a marked decrease in red cell deformability and distortion of the cell into the classic crescent or sickle shape. Red cells become inflexible and impair blood flow through the microvasculature. This leads to tissue and organ ischemia and reperfusion injury, with secondary inflammatory, thrombotic and oxidant stress.[5,6]

The two most common acute complications of SCD are vaso-occlusive pain crisis (VOC) and the acute chest syndrome (ACS) which is described in detail previously.[7] Acute increases in pulmonary pressures and right heart failure are common during severe VOC and more so during the ACS.[8] In addition, adults with SCD develop progressive vasculopathy, characterized by pulmonary artery endothelial dysfunction, intimal and smooth muscle and adventitia proliferation leading to PH.[9,10]

## Prevalence and Hemodynamic Characteristics of Pulmonary Hypertension in Sickle Cell Disease

Pulmonary hypertension is an increase in pulmonary artery pres-

**Table1. Hemodynamic definitions of pulmonary hypertension as defined by the American College of Cardiology**

| Definition | Hemodynamic Characteristics |
|---|---|
| PH | mPAP ≥25 mm Hg |
| Pre-capillary-PH or PAH | mPAP ≥25 mm Hg; PAWP ≥15 mm Hg; PVR >3 Wood units |
| Post-capillary-PH or PVH | mPAP ≥25 mm Hg; PAWP >15 mm Hg |
| Passive post-capillary-PH or PVH | TPG <12 mm Hg or DPG <5 mm Hg; PVR <3 Wood Units |
| Reactive post-capillary-PH or PVH | TPG ≥12 mm Hg or DPG ≥5 mm Hg; PVR >3 Wood units |

mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PAH, pulmonary arterial hypertension; PVH, pulmonary venous hypertension; PVR, pulmonary vascular resistance; TPG, transpulmonary gradient (mPAP-PAWP); DPG, diastolic pulmonary gradient (dPAP-PAWP)

sure that can lead to progressive right heart failure and death.[11] Pulmonary hypertension is defined as a mean pulmonary artery pressure (mPAP) ≥25 mm Hg in resting state as measured by RHC.[12] Hemodynamic definition of PH and subtypes as defined by the American College of Cardiology are summarized in Table 1. In SCD, PH may be: 1) pre-capillary (pulmonary arterial hypertension); 2) post-capillary (pulmonary venous hypertension); and 3) hemodynamics features of both pre- and post-capillary PH.[13,14] Pulmonary arterial hypertension (PAH) is a subgroup of PH, characterized hemodynamically by mPAP ≥ 25 mm Hg with a normal left heart filling pressure and elevated pulmonary vascular resistance (PVR) of 3 Wood units (WU) and higher.[12,15] Pulmonary venous hypertension (PVH) is another subgroup of PH mainly due to left heart disease. Post capillary PH can be passive (an increase in LVEDP is transmitted upstream to mPAP) if the transpulmonary pressure gradient (TPG [mPAP-PAWP difference]) is normal (12 mm Hg or lower)[16] or the diastolic pulmonary pressure gradient (DPG, dPAP-PAWP difference]) is normal (5 mm Hg or lower).[17] Post capillary PH is reactive (a chronic increase in LVEDP may induce pulmonary vascular remodeling leading to increased mPAP) if the TPG is >12 mm Hg[16] or DPG is >5 mm Hg[15,17] (Table 1).

Recent RHC studies[14,18-20] reported that 6.2%–10.4% of adults with SCD had PH of all types (Table 2). In the study from the United States,[14] PH of any kind was present in 10.4%, which was similar to the study from Brazil (10%),[19] and slightly higher than seen in a study from France,(6.2%),[18] possibly due to the exclusion of patients with severe renal, lung, and liver disease from the latter cohort. Pre-capillary PH occured in approximately 40%-45% of those with PH in SCD.[14,18] This prevalence would place SCD-PH as second only to scleroderma (12%) among associated conditions under World Health Organization (WHO) group I PAH,[21] and comparable to portopulmonary hypertension (1% to 6%),[22] and higher than HIV infection (.5%).[23]

Pre-capillary PH associated with SCD is defined similarly to WHO group I PAH (mPAP≥ 25 mm Hg, PAWP or LVEDP ≤ 15 mm Hg, and increased PVR). In WHO group I PAH, increased PVR is defined ≥ 3 Wood units;[12] however, the American Thoracic Society (ATS) consensus guidelines recommend a PVR ≥2 Wood units as indicative of a high PVR in adults with SCD because of anemia-induced elevation of their cardiac output and reduction in their blood viscosity, which resulted in a lower baseline PVR than observed in non-anemic patients.[17,24]

Some patients with SCD also have hemodynamics with features of both pre- and post-capillary PH. This is characterized by mPAP ≥25 mm Hg, a PAWP > 15 mm Hg, and an increased PVR. These patients often have an elevated TPG and DPG reflective of reactive pre-capillary PH.[14]

## Clinical Classification of Pulmonary Hypertension Associated with Sickle Cell Disease

A clinical classification was established in order to group together different categories of PH sharing similar pathological findings, hemodynamic characteristics and therapeutic response. Five groups of disorders that cause PH were identified: PAH (WHO group I); PH due to left heart disease (WHO group II); PH due to chronic lung disease and/or hypoxia (WHO group III); chronic thromboembolic PH (WHO group IV); and PH due to unclear multi-

factorial mechanisms (WHO group V).[25] The classification of SCD-PH has evolved during the successive PH world meetings: In the Evian classification,[26] it was placed in Group IV, in the Venice and Dana Point,[27] it was shifted to Group I and in the Nice classification, it was shifted to Group V.[25] The reclassification of SCD-PH as Group IV, Group I, and now as Group V stresses the need to define PH subgroups and conduct further research in these patients.[24]

## Diagnosis of Pulmonary Hypertension in Sickle Cell Disease

The diagnostic evaluation of a SCD patient with suspected PH is similar to that in the non-SCD patient and should follow the evidence-based consensus guidelines for the diagnosis and management of SCD-PH.[24] Diagnostic evaluation includes a history, physical examination, Doppler-echocardiography (DE), CAT scan and ventilation-perfusion imaging to exclude thromboembolic disease, laboratory testing (such as antinuclear antibody, hepatitis panel, HIV status, thyroid stimulating hormone level), and functional assessments of exercise tolerance with the six-minute walk test (6MWT), and RHC for definitive diagnosis.

SCD patients with symptoms that may indicate the presence of PH should be evaluated initially by Doppler echocardiography (DE).[24] The cardinal signs of PH are tricuspid regurgitant velocity (TRV) >2.5 m/second, suggestive of elevated right ventricular systolic pressure, right ventricular (RV) dilation or dysfunction, and flattening of the interventricular septum.[28] Overall, DE is reliable in the presence of severe PH, but is not a sensitive marker in mild-to-moderate PH. This has been illustrated by a study of patients with SCD with a PH prevalence of 6%; the positive predictive value for PH was only 25% among patients with a TRV of at least 2.5 m/second, although this improved to 64% when a TRV >2.9 m/second was used as the threshold instead.[18]

Serum N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), a marker of right and left ventricular strain is another noninvasive test that is imperfect diagnostically.[29] Elevated N-TproBNP concentrations was predictive of increased TRV and associated with increased mortality,[30-32] but most studies in SCD that evaluated the diagnostic characteristics of NT-pro-BNP were limited because they used an elevated TRV as the reference standard for PH, rather than RHC hemodynamic measurements. The positive predictive value of DE also improves by combining it with other tests such as NT-pro-BNP and the 6MWT.[18]

The 6MWT has been a key mea-

**Table 2. Hemodynamic characteristics by pulmonary hypertension status in sickle cell patients**

| Country of study | France[18] | | Brazil[19] | | USA[20] | |
|---|---|---|---|---|---|---|
| Total patients screened | 385 | | 80 | | 531 | |
| Underwent RHC | 96 | | 26 | | 84 | |
| PH- Status n (%) | PH =24 (6%) | No PH =72 | PH=8 (10%) | No PH=18 | PH=55 (10.4%) | No PH=29 |
| sPAP, mm Hg | 44 ± 7 | 28 ± 4 | 48 ± 13 | 29 ± 5 | 58 ± 15 | 31 ± 6 |
| dPAP, mm Hg | 19 ± 6 | 12 ± 3 | Not given | Not given | 26 ± 7 | 13 ± 4 |
| mPAP, mm Hg | 30 ± 6 | 19 ± 3 | 33 ± 9 | 19 ± 3 | 36 ± 9 | 19 ± 4 |
| PAWP, mm Hg | 16 ± 7 | 11 ± 3 | 16 ± 6 | 13 ± 2 | 16 ± 5 | 11 ± 3 |
| Cardiac output, L/min | 9 ± 2 | 8 ± 2 | 5 ± 2Ǐ | 5 ± 1Ǐ | 8 ± 3 | 9 ± 2 |
| PVR, dynes.s.cm-5 | 138 ± 58 | 72 ± 26 | 179 ± 120 | 64 ± 48 | 227 ± 149 | 72 ± 37 |
| Precapillary PH, n (%) | 11 (2.7%) | - | 3 (3.75%) | - | 31 (6%) | - |
| Postcapilary PH, n(%) | 13 (3.3%) | - | 5 (6.25%) | - | 24 (4.5%) | - |
| TRV, m/s | 3.1 ± 0.4 | 2.7 ± 0.2 | Not reported | Not reported | 3.3 ± 0.5 | 2.9 ± 0.4 |
| NT-proBNP, pg/mL | 961 ± 2067 | 95 ± 77 | Not reported | Not reported | 153 (70-470) | 58(29-123) |
| WHO FC III or IV, % | 7% | 38% | Not reported | Not reported | 33% | 14% |
| 6MWD, meter | 404 ± 94 | 527 ± 62 | 460 ± 150 | 511 ± 78.9 | 358 ± 115 | 437 ± 108 |
| Mortality - (%) | 12.5% | 1.4% | 38% | 5.5% | 36% | 13% |

CVP, central venous pressure; dPAP, diastolic pulmonary artery pressure; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RHC, right heart catheterization; sPAP, systolic pulmonary artery pressure; TRV, tricuspid regurgitant jet velocity; WHO FC, World Health Organization functional class; 6MWD, Six-minute walk distance; Ǐ, cardiac index-L/m$^2$

**Table 3. Hemodynamic predictors of mortality in sickle cell associated pulmonary hypertension**

| Variable | Adjusted HR (95% CI) | *P* |
|---|---|---|
| mPAP, per 10 mm Hg | 1.61 (1.05–2.45) | .027 |
| dPAP, per 10 mm Hg | 1.83 (1.09–3.08) | .022 |
| dPAP − PAWP, per 10 mm Hg | 2.19 (1.23–3.89) | .008 |
| TPG, per 10 mm Hg | 1.78 (1.14–2.79) | .011 |
| PVR, per Wood unit | 1.44 (1.09–1.89) | .009 |
| sPAP, per 10 mm Hg | 1.30 (.99–1.71) | .055 |

CI, confidence interval; dPAP, diastolic pulmonary artery pressure; dPAP − PCWP, diastolic pulmonary artery pressure minus pulmonary artery wedge pressure; HR, hazard ratio; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; 6MWD, 6-min-walk distance; sPAP, systolic pulmonary artery pressure; TPG, transpulmonary gradient (mean pulmonary artery pressure minus pulmonary artery wedge pressure).

sure of prognosis and response to therapy in PAH.[33] In SCD, although concomitant musculoskeletal or joint involvement will reduce the reliability of the 6MWT, the distance walked correlates with PH severity and improved with a favorable therapeutic response.[13] Given its ease, noninvasive nature, and low cost, 6MWT is useful to follow the course of the disease and assess response to therapy.

The etiology of SCD-PH is unclear and is often multifactorial including hemolysis, dysregulated nitric oxide (NO) metabolism, hypoxia, oxidative stress, high cardiac output, left-heart disease, chronic thromboembolism, asplenia, renal insufficiency, vasoactive mediators such as endothelin -1 and genetic factors.[9,10,34-36] The relative contribution of each of these mechanisms to SCD-PH in individual patients is variable and remains unknown.

## Survival and Hemodynamic Predictors for Mortality in SCD-PH

SCD-PH is characterized by relatively modest elevations of mPAP, PVR and a high cardiac output.[13,37] Despite these seemingly mild hemodynamic findings, any level of PH in these severely anemic patients portends a poor prognosis. Consistent with this observation, patients with SCD with PH can have histopathological changes more severe than might be expected from relatively modest hemodynamic abnormalities.[14] All the recent RHC studies[18-20] reported PH as a risk factor for early mortality. In the US study, survival estimates for the SCD patients with PH vs those without PH were: 89% vs 100% at 1 year; 76% vs 93% at 3 years; and 63% vs 83% at 5 years from time of diagnosis by RHC.[14] In a multivariate model, several hemodynamic variables known to characterize severity of pre-capillary PH were associated with mortality (Table 3).[14]

In patients with idiopathic pulmonary arterial hypertension (IPAH), increased mPAP, increased CVP, and decreased cardiac index predicted increased risk of death.[38] Some of these hemodynamic variables were not independently associated with mortality in SCD-PH, suggesting that there may be a different mode of demise in SCD-PH. Additionally, the acute increase in pulmonary artery pressure in the sickle cell VOC[39] and ACS[8] might be an additional risk factor in these SCD-PH patients with diminished functional reserve. It is important to point out that, TPG and PVR are independent risk factors for death, suggesting that these measures may be more relevant indices of pulmonary vascular dysfunction in SCD patients with PH. The prognostic value of PVR and TPG is shared with scleroderma associated pre-capillary PH,[40] PH after heart transplantation,[41] and portopulmonary hypertension after liver transplantation.[42]

## Treatment of Pulmonary Hypertension in Sickle Cell Disease

### Sickle Cell Disease Specific Therapy

In 2014, the American Thoracic Society (ATS) published an evidence-based consensus guideline for management of SCD-PH.[24] Pulmonary hypertension diagnosed by RHC is an independent risk factor for early mortality in adults with SCD. Epidemiologic studies have also consistently shown that increased TRV,[43-45]

and increased serum NT-pro-BNP level, are all independent risk factors for mortality in SCD adults.[30]

SCD patients identified at high risk of death (ie, TRV ≥ 2.5 m/s, NT-pro-BNP ≥ 160 pg/ml, or RHC-confirmed PH) should have intensive SCD-specific therapies to reduce the severity of hemolytic anemia with hydroxyurea (HU), and in patients who cannot tolerate HU, through chronic red blood cell transfusion regimens. Although the use of HU and chronic transfusions have not been specifically tested in placebo-controlled trials in patients with SCD-PH, HU increases the concentration of fetal hemoglobin, often reduces anemia, decreases the frequency of VOC and ACS and improves survival for HbSS patients.[46] It is widely accepted that HU is indicated for patients with SCD who have the HbSS genotype and at least three VOC per year or at least one episode of ACS.[47] The ATS practice guideline[24] applied the same recommendation to patients with an increased risk for mortality. This reflects the recognition that VOC, ACS, PH, elevated TRV, and elevated NT-pro-BNP are all established independent risk factors for death among patients with SCD.

Patients identified as high risk of death should also be screened for co-morbid factors that are treatable, such as venous thromboembolism and obstructive sleep apnea. Other supportive general measures include treating hypoxemia with supplemental oxygen to maintain an arterial oxyhemoglobin saturation of at least 90% at rest, with exertion, and during sleep.[48] Diuretics are used to treat right ventricular volume overload,[48] but this must be done carefully to minimize the risk of volume depletion–induced erythrocyte sickling.[24]

### Pulmonary Arterial Hypertension Targeted Therapy

PAH targeted therapy refers currently to treatment with prostacyclin agonists, endothelin receptor antagonists, soluble guanylate cyclase stimulators or phosphodiesterase-5 inhibitors. The literature evaluating PAH therapy in SCD-PAH is limited. Two randomized controlled trials compared treatment with the endothelin receptor antagonist, bosentan, to placebo in patients with SCD with RHC-defined precapillary PH (the ASSET-1 trial) or postcapillary PH with a PVR of at least 100 dyn seconds $cm^{-5}$ (the ASSET-2 trial).[49] After randomization of only 14 patients in ASSET-1 and 12 patients in ASSET-2, the trials were prematurely terminated because of sponsor's withdrawal of support for the study. The third trial, Walk-PHaSST (Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Therapy),[50] compared the safety and efficacy of sildenafil with that of placebo in patients with SCD with a TRV of at least 2.7 m/second. After 74 (of a targeted 132) patients were enrolled, the study was prematurely discontinued because of an increase in serious adverse events in the sildenafil group, primarily hospitalization for pain.

These trials were insufficient to determine whether patients with SCD-PAH would benefit from targeted PAH specific therapy for two main reasons. First, the trials collectively included few patients with an elevated PVR and normal PAWP by RHC. Secondly, as a result of the small sample size and early study termination, the estimated effects were imprecise.

In WHO group I PAH, it has been well-established that targeted PAH therapy consistently improves exercise capacity, functional status, hemodynamics, and outcomes.[51-53] There are four case series in which patients with SCD with RHC-confirmed precapillary PH received targeted PAH therapy with bosentan, sildenafil, and/or epoprostenol. Targeted PAH therapy was associated with improvement in exercise capacity, with the 6MWD increasing 41 to 144 m beyond baseline.[54-56] There were also improvements in the mPAP, PVR, and cardiac index, although these parameters were measured in only a few patients.[56] The magnitude of the benefits was greatest among symptomatic patients.

For selected patients with RHC-confirmed PH who have elevated PVR (PVR≥2 Wood units) and normal PAWP, the ATS guidelines recommend either prostacyclin agonist or endothelin receptor antagonist.[24] Overall, management of SCD-PH patients is complex and it is recommended that these patients be referred to a center with expertise in these disciplines.

## Summary

Pulmonary hypertension in the setting of SCD is common, disabling, and associated with a high mortality. SCD-PH hemodynamics may be pre- or post-capillary and only RHC can confirm the diagnosis and makes it

possible to accurately distinguish between them. Accurate hemodynamic stratification is important before initiating therapy as well as before enrolling patients in PAH clinical trials.

SCD-PH is characterized by a lower PVR compared with Group I PAH due to anemia-induced elevation of cardiac output and reduction in blood viscosity resulting in a lower pre-morbid PVR. Hemodynamic parameters such as mPAP, TPG, DPG and PVR are independently associated with increased risks of death suggesting that these measures may be more relevant indices of pulmonary vascular dysfunction in patients with SCD-PH. The distinct and complicated hemodynamic features of SCD-PH have helped us to understand the disease to some degree but many questions remains unanswered. Such questions are: 1) what is the underlying pathophysiology of SCD-PH? 2) Which biomarker suggests early pulmonary vascular disease in SCD? 3) What is the relationship of pulmonary vascular disease and cardiac function in SCD-PH? 4) Do PAH targeted treatment improves outcomes in SCD? 5) Does intensive SCD therapy such as use of hydroxyurea or chronic red cell transfusions, in those with PH improve outcomes? 6) What are the mechanisms leading to early death in SCD-PH?

Screening for PH in symptomatic SCD patients for early diagnosis and use of disease-modifying therapy are recommended. Much needs to be done to study the natural history of this complication across the life span of SCD patients in order to better understand the potential impact of screening and prevention. Despite the major impact on morbidity and mortality, the exact etiology of SCD-PH and the safety and efficacy of PAH targeted therapy is largely unknown. The current treatment of SCD-PAH is based on expert opinion due to limited evidence, highlighting the critical need for randomized clinical trials in this area. To narrow the knowledge gap in this field, a collaborative effort between the different disciplines from internal medicine, pulmonary, hematology and cardiology will be necessary.

## Future Directions

Five-year survival of adults with SCD-PH remains unacceptably poor at 37%. We hope to see improved strategies of prevention and management of PH in SCD in the coming years. To achieve this, we anticipate mechanistic studies focusing on identifying underlying pathobiology and randomized clinical trials of effective therapy of SCD-PH involving hemodynamically well-characterized patients. Better understanding of the underlying mechanisms and identifying the risk factors for SCD-PH early could guide preventative strategies, improve diagnosis, and allow appropriate interventions and outcomes need to be determined. Screening for PH with subsequent implementation of treatment guided specifically by PAH in SCD changes patient outcomes need to be determined in randomized clinical trials.

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### Conflict of Interest

No conflicts of interest to report.

### Author Contributions

Research concept and design: Mehari; Acquisition of data: Mehari; Data analysis and interpretation: Mehari, AV Thomas, AN Thomas, Johnson; Manuscript draft: Mehari, AV Thomas, AN Thomas, Johnson; Acquisition of funding: Mehari; Administrative: Mehari, AV Thomas, AN Thomas, Johnson

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