REGULAR ARTICLE

The Myriad Presentations of Sickle Cell Disease-Related Pulmonary Hypertension

Clare C. Prohaska, MD
Division of Pulmonary, Critical Care, Sleep, and Occupational Medicine
Department of Medicine
Indiana University
Indianapolis, IN

Roberto F. Machado, MD
Division of Pulmonary, Critical Care, Sleep, and Occupational Medicine
Department of Medicine
Indiana University
Indianapolis, IN

Background: Sickle cell disease (SCD) is characterized by repeated episodes of hemolysis and vaso-occlusion. Hemolysis is a risk factor for the development of pulmonary hypertension (PH), and currently SCD-related PH is classified as World Health Organization group 5 PH. Patients with SCD-related PH have unique hemodynamics, comorbidities, and phenotypes that may contribute to the development of PH.

Implications for Clinicians: SCD-related PH is defined as a mean pulmonary artery pressure >20 mm Hg, a pulmonary artery occlusion pressure ≤15 mm Hg and relatively low pulmonary vascular resistance (PVR) (>160 dynes·sec/cm^5 rather than the typical definition of ≥240 dynes·sec/cm^5), an important distinction because of a baseline high-cardiac output state in the setting of chronic anemia and low vascular resistance. Diastolic dysfunction is common, and right heart catheterization is warranted to determine if combined precapillary and postcapillary PH is present. Thromboembolism is common among patients with SCD, and screening for chronic thromboembolic pulmonary hypertension is essential. There are few studies evaluating advanced therapies in this population. The mainstay of treatment includes targeting correction of their primary hemoglobinopathy as well as aggressive management of underlying comorbid conditions.

Conclusions: SCD-related PH is common among patients with SCD and is associated with increased mortality. A high index of suspicion is warranted during evaluation to identify all potential factors that may be contributing to disease.

INTRODUCTION

Sickle cell disease (SCD), one of the most common genetic diseases in the world, is caused by a E6V missense mutation in the β globin gene leading to the formation of sickle hemoglobin (HbS), a variant of normal adult hemoglobin (HbA).[1,2] In hypoxic conditions, HbS abnormally polymerizes, leading to sickling of erythrocytes; the extent of sickling is the primary determinant of the severity of SCD.[3] SCD is characterized by 2 main pathologic events: hemolysis and recurrent vaso-occlusive crises. Over time, repeated episodes contribute to decreased quality of life, multiorgan system failure, and premature death. The acute chest syndrome and pulmonary hypertension (PH) are the most common causes of death in this population.[4-7]

PH is currently defined as a mean pulmonary artery pressure (mPAP) measured by right heart catheterization (RHC) as >20 mm Hg.[8] Individuals with SCD may develop PH with primary vascular involvement (World Health Organization [WHO] group 1, or pulmonary arterial hypertension [PAH]), secondary to left heart disease (group 2 PH), secondary to interstitial lung disease or pulmonary fibrosis (group 3 PH), or because of chronic thromboembolic PH (CTEPH, or group 4 PH). Because of these myriad presentations, PH related to SCD is currently listed in group 5 in the clinical classification of PH.

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Epidemiology and Prevalence of SCD

Between 300 000 and 400 000 individuals are born annually with SCD worldwide,[9] and around 100 000 individuals in the United States live with the disease.[10] Individuals with one copy of HbS are protected against severe forms of *Plasmodium falciparum* malaria; therefore, the βs allele is found more frequently in sub-Saharan Africa, parts of the Mediterranean, the Middle East, and India.[9,11,12] Approximately 1 in 360 African American newborns has SCD.[13] Despite nearly 100 years of research, the natural history of SCD remains poorly described. Mortality rates have improved over the past 60 years, but the median age at death remains unacceptably low: between 42 to 53 years for men and 48 to 58.5 years for women.[5,14,15]

PATHOPHYSIOLOGY

Hemoglobin is a tetrameric protein comprised of various combinations of

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globin subunits. HbA, the most abundant hemoglobin, is comprised of two α and two β globin subunits; with a single point mutation in subunit β, HbS is produced. Individuals heterozygous for sickle hemoglobin are considered to have sickle cell trait rather than SCD. Individuals homozygous for sickle hemoglobin have sickle cell anemia.[16] Other forms of SCD include heterozygous combinations of HbS with hemoglobin C, HbS with β-thalassemia or HbS with other beta-globin variants; therefore, SCD is an umbrella term used to describe any form of disease in which there is enough HbS to cause significant intracellular sickling.[17]

Under hypoxic conditions, cells containing homozygous sickle hemoglobin polymerize, changing the shape and physical properties of the erythrocyte, leading to hemolysis and repeated episodes of vaso-occlusion. Compared to HbA, HbS has reduced oxygen affinity; this exacerbates polymerization of HbS. Through interactions with deoxygenated beta-globin subunits, hemoglobin oxygen affinity is further reduced.[18] Low HbS oxygen affinity kinetically favors an increase in the fraction of deoxygenated HbS, a form that readily polymerizes, which further promotes HbS polymerization and sickling of erythrocytes. HbS polymerization correlates exponentially with the concentration of HbS within the erythrocyte. Repeated episodes of HbS polymerization and sickling in low pO2 conditions and unsickling in high pO2 conditions may lead to severe alterations in erythrocyte membrane structure and function, which eventually result in an irreversibly sickled cell.[19-22]

Hemolysis releases plasma-free hemoglobin that inactivates nitric oxide (NO), an intrinsic vasodilator, as well as arginase-1, which depletes L-arginine, the substrate for NO synthesis.[23-25] As a result, there is decreased NO bioavailability and *resistance* to NO-dependent vasodilation.[25] There is also accumulation of redox-active heme and iron from lysed red blood cells, which contributes to the generation of reactive oxygen species that can exacerbate thrombosis and vascular proliferation.[26]

There is a correlation between the rate of hemolysis and levels of procoagulant factors in blood in patients with SCD.[27-29] Hemolysis and decreased NO bioavailability induce platelet and tissue factor activation and thrombin generation, which induce a procoagulant state.[30,31] Patients with SCD are at high risk for pulmonary embolism,[32] and microthrombotic and/or thromboembolic lesions are common findings as postmortem examination in patients with SCD.[33,34]

Splenectomy in SCD

Many individuals with SCD have functional asplenia. In fact, splenectomy has been identified as an independent risk factor for the development of PH, particularly in patients with underlying hemolytic disorders.[35-38] Loss of splenic function may also trigger platelet activation, promoting pulmonary microthrombosis and red cell adhesion to the endothelium.[39] Furthermore, after splenectomy, the rate of intravascular hemolysis increases.[29]

The Effect of Anemia on Cardiac Output

Hemolysis and anemia appear to have a synergistic effect on the heart and systemic and pulmonary vasculature. Anemia leads to decreased blood oxygen content, which causes a high cardiac output state; this is necessary to maintain oxygen delivery and is characterized by increased stroke volume, primarily from decreased blood viscosity. In this high-output state, patients with SCD are more sensitive to changes in hemoglobin concentration and less able to compensate to stressors from a cardiac output standpoint. Elevated cardiac output leads to the development of ventricular dilation, hypertrophy, and wall stress.[40-44] If anemia is corrected via transfusion, cardiac output returns to normal and systemic vascular resistance increases.[42]

In individuals with severe anemia, particularly those with underlying cardiopulmonary disease, anemic hypoxia can occur because of the decreased ability of blood to transport oxygen and participate in gas exchange. There is a strong correlation between the severity of hemolytic anemia and decreasing arterial hemoglobin saturation, likely because of increased cardiac output and altered perfusion of the pulmonary vasculature, which may lead to impaired ventilation-perfusion matching.[45,46]

Two Primary Phenotypes of SCD

There appears to be 2 distinct SCD clinical phenotypes: a vaso-occlusive phenotype and a hemolytic phenotype.[47] Although these distinctions occur on a spectrum and vary at the individual patient level, they are helpful to approach individuals with SCD from a clinical perspective. The vaso-occlusive phenotype is characterized by persistent leukocytosis, higher hemoglobin levels and bony pain, in which case recurrent episodes of acute chest syndrome tend to occur. The hemolytic phenotype is characterized by chronic kidney disease, cutaneous leg ulcers, priapism, and strokes, as well as vascular dysfunction, in which case PH tends to develop more frequently.[48]

Hemodynamic Profiles of PH in SCD

During the Sixth World Symposium in Pulmonary Hypertension the definition of precapillary PH was changed to a mPAP > 20 mm Hg and PVR ≥ 240 dynes·sec/cm^5.[8,49,50] Because of chronic anemia, patients with SCD have baseline increases in cardiac output and low vascular resistances. At baseline, PVR in patients with SCD ranges from 68 to 74 dynes·sec/cm^5, as compared to nonanemic healthy volunteers of 80 to 120 dynes·sec/cm^5. As a result, a PVR > 160 dynes·sec/cm^5 has been proposed as abnormal in patients with SCD.[51]

Studies using the former definition of PH (mPAP ≥ 25 mm Hg) suggest that the prevalence of PH in SCD is 6% to 11%.[52-55] (Table 1) Given the large body of literature published prior to this updated definition of disease, a significant number of individuals with SCD could be classified as having SCD-related PH. Approximately half of patients have precapillary PH (defined as mPAP ≥ 25 mm Hg and pulmonary artery occlusion pressure [PAOP] ≤ 15 mm Hg), and half have postcapillary PH (defined as mPAP ≥ 25 mm Hg and PAOP > 15 mm Hg).[52-56] Another clinical and hemodynamic phenotype that is common in SCD is one in which group 2 PH is present but the pulmonary vasculature

Table 1. Hemodynamic profiles in SCD patients with and without pulmonary hypertension[a]

Country of study	Parent et al		Fonseca et al		Mehari et al	
Number 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
mPAP, mm Hg	30 ± 6	19 ± 3	33 ± 9	19 ± 3	36 ± 9	19 ± 4
PAOP, mm Hg	16 ± 7	11 ± 3	16 ± 6	13 ± 2	16 ± 5	11 ± 3
CO, L/min	9 ± 2	8 ± 2	5 ± 2[b]	5 ± 1[b]	8 ± 3	9 ± 2
PVR, dyn·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%)	-
Postcapillary PH, n (%)	13 (3.3%)	-	5 (6.25%)	-	24 (4.5%)	-
Mortality (%)	12.5	1.4	38	5.5	36	13

Abbreviations: SCD, sickle cell disease; RHC, right heart catheterization; PH, pulmonary hypertension; mPAP, mean pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure; PVR, pulmonary vascular resistance.

[a]Adapted from Parent et al[53], Fonseca et al[54], and Mehari et al.[55]
[b]Cardiac index (L/min/m^2).Table 2. Univariate and multivariate analysis of mortality risk factors in SCD.[a]

has been remodeled and the transpulmonary gradient (mPAP-PAOP) and PVR rise.[57,58] Therefore, although the mPAP is >20 mm Hg and PAOP is >15 mm Hg, the PVR is ≥240 dynes·sec/cm^5; this is now termed combined precapillary and postcapillary PH.[8]

PH in SCD may occur secondary to isolated pathologic remodeling of the pulmonary arterioles, beginning with vasoconstriction, hyperplasia of intima and smooth muscle and progressing to severe angioproliferation, occlusion, and recanalization, termed the plexiform lesion.[59] When disease is restricted to the pulmonary arterioles, mean pulmonary pressures increase but left ventricular end-diastolic pressures (measured on RHC by PAOP) are normal (≤15 mm Hg). According to autopsy studies, pulmonary vascular lesions characteristic of precapillary PH have been found in one-third to two-thirds of patients with SCD.[33,34]

Group 2 PH, defined by mPAP > 20 mm Hg and PAOP > 15 mm Hg, with a normal PVR, arises from left heart disease. In chronic anemia, the left ventricle compensates with an increase in stroke volume and chamber dilatation, leading to increased wall stress and an increase in left ventricular mass. This hypertrophy leads to impaired filling, which is characteristic of diastolic dysfunction, also known as heart failure with preserved ejection fraction.[41,43] Heart failure with reduced ejection fraction is much less common in patients with SCD, but is still an important cause of group 2 PH. Many patients with PH due to diastolic dysfunction also have an increased transpulmonary gradient consistent with combined precapillary and postcapillary PH. Importantly, diastolic dysfunction is associated with decreased exercise capacity and independently associated with increased mortality in individuals with SCD, despite adjusting for tricuspid regurgitant velocity (TRV).[40,41]

The majority of patients with SCD have hemodynamic profiles consistent with group 1 and group 2 disease. High-output heart failure may occur because of longstanding elevated cardiac output in the setting of anemia, although this is a rare etiology of PH. Advanced lung disease and pulmonary fibrosis leading to PH (group 3 PH) is exceedingly rare, even if patients develop recurrent episodes of acute chest syndrome (ACS) over time. However, patients should be screened and treated for obstructive sleep apnea or nocturnal hypoxemia if present.

Given that patients with SCD are at high risk of developing thromboembolism, they are at higher risk for developing CTEPH (group 4 PH), characterized by recurrent pulmonary thromboemboli followed by fibrotic remodeling of the occluded pulmonary vasculature.[59] Scintigraphic evidence suggestive of CTEPH occurs in approximately 5% of patients with SCD and severe PH,[60] and may be associated with more severe hemodynamic abnormalities, lower exercise capacity, and higher mortality.[61] Identification of CTEPH is important as these patients require lifelong anticoagulation. Specific medications may be approved for therapeutic use,[62] and surgical options may be available, including pulmonary artery balloon angioplasty or pulmonary endarterectomy.[63-67]

DIAGNOSTIC EVALUATION

The development of PH appears to increase with advancing age and is a major cause of early death. Diagnostic evaluation should assess for conditions that may also contribute to the development of PH, including iron overload, chronic liver disease, HIV infection, nocturnal hypoxemia, and pulmonary thromboembolism. Plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) can identify patients with SCD at higher risk of PH, lower exercise capacity and increased mortality risk.[68-70]

Cardiac ultrasound is used to screen for PH and right heart failure, and the pulmonary artery systolic pressure can be estimated by measuring the TRV.[6] A value of ≥2.5 m/s is 2 standard deviations above the mean for patients aged 35 to 40 years, and a value ≥3.0 m/s is 3 standard deviations above the popula-

tion mean. Prospective and retrospective studies have shown that using a TRV of 2.5 m/s as a cutoff for elevated pulmonary artery systolic pressure estimates that 20% to 30% of individuals with SCD meet the criteria for PH, and approximately 8% to 10% have values 3 standard deviations above the normal mean (TRV ≥ 3 m/s).[6,52] These findings have been reproduced in multiple studies,[53,54,71,72] and it is accepted that even a mildly elevated TRV is associated with increased mortality.[6,71,73] However, a RHC remains the gold standard to confirm the diagnosis and hemodynamic etiology of PH.[74]

A 6-minute walk test inversely correlates with the severity of PH.[40,60] Although patients with PH may have less severe abnormalities in their hemodynamic profiles, their 6-minute walk test and WHO functional class may be severely abnormal, and these abnormalities are associated with increased mortality.[55] Pulmonary functional tests should also be pursued, as most adults with SCD develop abnormal pulmonary function, typically mild restriction and abnormal diffusing capacity due to mild pulmonary fibrosis. These defects may be slightly worse among individuals with SCD who also have PH,[75-78] but are rarely a major contributor to the development of PH. A ventilation-perfusion scan is also necessary to rule out evidence of CTEPH or chronic pulmonary thromboembolic disease and is superior to computed tomography pulmonary angiography.[61] Computed tomography chest may show mosaicism of lung parenchyma, demonstrating areas of hypoattenuation and decreased blood flow due to obstructed vasculature and decreased blood flow, juxtaposed to areas of normal lung parenchyma with normal blood flow.

Screening for Cardiovascular Disease

The American Thoracic Society published guidelines recommending that adult patients with SCD undergo screening echocardiography and/or NT-proBNP testing to assess the risk of death and of having PH for further diagnosis and intensification of sickle cell-specific therapies.[51] (Figure 1) Patients with a TRV value of 2.5 to 2.9 m/s are further risk stratified by 6-minute walk testing and plasma NT-proBNP testing, with abnormal values suggesting the need for RHC. Patients with values >2.9 m/s should undergo RHC, particularly if there is evidence of right heart dysfunction. Patients with PH should be screened for CTEPH. If patients develop symptoms suggestive of PH, initial screening with echocardiography and RHC may later be pursued.

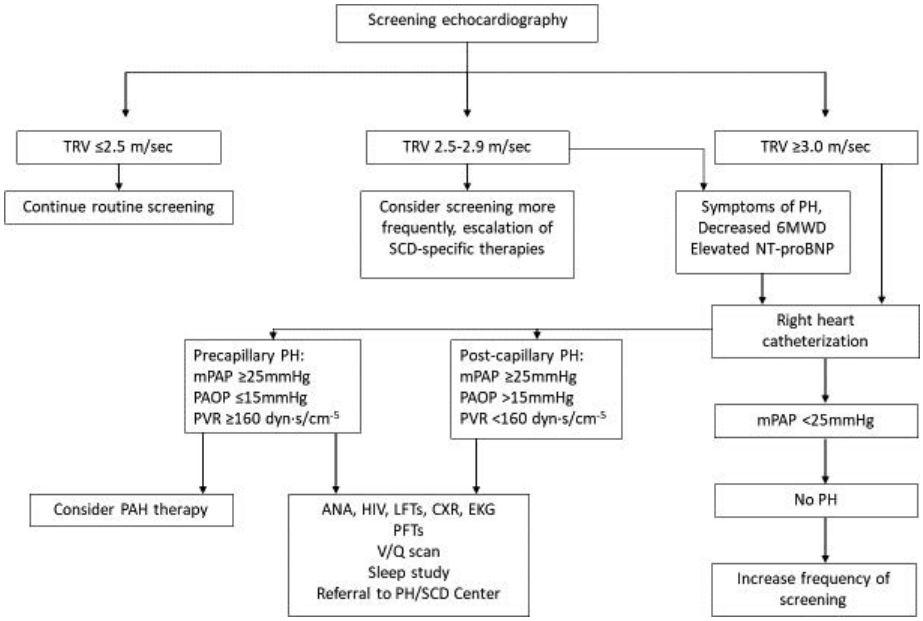

Figure 1: Diagnostic algorithm for evaluating PH in SCD. Adapted from Ghofrani et al.[63]

Mortality

The first study establishing a link between PH based on RHC and increased mortality was published in 2003. This study described a 55% mortality over 23 months and found that mPAP was inversely related to survival. Furthermore, for every increase in mPAP of 10 mm Hg, there is a 1.7-fold increase in the hazard ratio of death in patients with SCD.[73] Mortality is significantly higher in patients with PH defined by RHC, with significant correlation between hemodynamic markers and increased risk of death.[52-55] (Table 2) This has been validated by multiple subsequent studies, which have also found that an elevated transpulmonary gradient, diastolic pulmonary gradient (pulmonary artery diastolic pressure-PAOP), PVR, NT-proBNP, WHO functional class, and lower 6-minute walk test were all associated with increased mortality.[55,69,71]

Treatment Options

Data are limited on specific management of patients with SCD and PH; most treatment recommendations are extrapolated from data derived from other forms of PH or expert opinion.[51] Generally, maximization of SCD-specific therapy, treatment of hypoxia with supplemental oxygen therapy and treatment of associated cardiopulmonary conditions (for example, HIV, iron overload, nocturnal hypoxemia, thromboembolic disorders, left ventricular disease, and chronic liver disease) are warranted. Chronic red blood cell transfusions have been shown to reduce pulmonary pressures and increase 6-minute walk distance and functional classification in patients with SCD and PH.[79]

In SCD patients with PAH, namely, patients with a mPAP ≥ 25 mm Hg, PAOP ≤ 15 mm Hg and relatively high PVR (>160 dynes·sec/cm^5), PAH-specific therapy may be considered. There are no long-term data on specific treatment of PH in SCD, and choice of agent is empirical and based on the safety profile of the medication and physician preference. Sildenafil and other phosphodiesterase 5 inhibitors function by inhibiting the metabolism of cyclic guanosine monophosphate, the second messenger that mediates the effects of NO. Sildenafil has been shown to im-

Table 2. Univariate and multivariate analysis of mortality risk factors in SCD[a]

Characteristic	Unadjusted HR (95% confidence interval)	*P* value	Adjusted HR (95% confidence interval)	*P* value
Age, per 10 yr	1.02 (0.76-1.38)	.89	-	-
sPAP, per 10 mm Hg	1.30 (1.06-43.6)	.048	1.30 (0.99-1.71)	.055
dPAP, per 10 mm Hg	1.91 (1.25-2.92)	.002	1.83 (1.09-3.08)	.022
mPAP, per 10 mm Hg	1.62 (1.17-2.24)	.003	1.61 (1.05-2.45)	.027
TPG, per 10 mm Hg	1.82 (1.28-2.61)	<.001	1.78 (1.14-2.79)	.011
PVR, per 1 Wood unit	1.35 (1.11-1.65)	.002	1.44 (1.09-1.89)	.009
PVRI, per 1 Wood unit/m^2	1.20 (1.08-1.33)	<.001	-	-
PP, per 10 mm Hg	1.29 (0.96-1.73)	.091	-	-
dPAP-PCWP, per 10 mm Hg	2.26 (1.43-3.58)	<.001	2.19 (1.23-3.89)	.008
CVP, per 10 mm Hg (n = 83)	1.36 (0.65-2.83)	.42	-	-
PCWP, per 10 mm Hg	0.97 (0.47-2.02)	.93	-	-
Cardiac output, L/min	0.98 (0.85-1.13)	.74	-	-
Cardiac index, L/min/m^2	0.87 (0.66-1.13)	.29	-	-
SVO2, % (n = 78)	0.98 (0.94-1.03)	.42	-	-
6MWD, m (n = 80)	0.56 (0.39-0.79)	<.001	-	-
WHO FC (III or IV vs I-II)	3.64 (1.64-8.05)	<.001	-	-

Abbreviations: 6MWD, 6 minute walk distance; CVP, central venous pressure; dPAP, diastolic pulmonary artery pressure; HR, heart rate; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PP, pulmonary artery pulse pressure; PVC, pulmonary artery capacitance; PVR, pulmonary vascular resistance; PVRI, pulmonary vascular resistance index; SCD, sickle cell disease; sPAP, systolic pulmonary artery pressure; SV, stroke volume; SVI, stroke volume index; SVO2, mixed venous oxygen saturation; SVR, systemic vascular resistance; TPG, transpulmonary gradient; WHO FC, World Health Organization functional class.

[a]Adapted from Mehari et al.[55]

prove pulmonary pressures and 6-minute walk distance in phase II studies,[80] but increased hospitalization due to painful crises was shown in one larger, randomized, double-blind, placebo-controlled trial.[56] Sildenafil is only recommended in patients with well-controlled and maximized SCD-specific therapy. Riociguat, a small molecule activator of soluble guanylate cyclase, is approved for the treatment of PAH and CTEPH, but its extrapolated use in individuals with SCD-related PH is limited to 1 case series of 6 patients.[62]

There is also limited published evidence with endothelin receptor agonists in the treatment of SCD-related PH. One retrospective study evaluating the use of ambrisentan and bosentan included 14 individuals with SCD-related PH found that therapy was well tolerated: there was a significant improvement in 6-minute walk distance, a trend toward lower BNP and TRV, and 3 individuals had decreases in their mPAP based on RHC. Therapy was stopped in 2 because of adverse reactions, but both tolerated the switch to the other endothelin-receptor agent.[81] However, the following year 2 randomized, double-blind, placebo-controlled studies were performed, the ASSET-1 and ASSET-2 trials.[82] Unfortunately, because of slow patient enrollment and site initiation, the studies were terminated prematurely. Preliminary analyses suggested that bosentan was well tolerated, with a trend toward increased CO and decreased PVR observed.

Prostacyclin-based therapies are the most effective agents for the treatment of traditional forms of PAH. Acutely, administration of epoprostenol decreases pulmonary artery pressure and PVR, and increases cardiac output.[73] Over time, prostacyclin-based therapy may reduce pulmonary pressure, increase 6-minute walk distance, and improve functional class.[83] However, its use remains off-label, with no prospective studies performed in patients with SCD.

Stem cell transplantation is the only curative option for individuals with SCD but is limited because of limited numbers of unaffected matched sibling donors and concerns regarding long-term toxicities.[84-88] Furthermore, bone marrow and lung transplantation have been shown to normalize pulmonary pressures and improve short-term outcome measures,[89,90] but may be associated with significant morbidity and mortality. Gene therapy remains an appealing option but remains limited in its application with further studies ongoing.[91,92]

CONCLUSIONS

Among individuals with SCD, PH is prevalent and remains a significant cause of morbidity and mortality. The underlying etiology of the development of PH in this population is complex and multifactorial, and a thorough workup is required to address all potential contributing disease states. Despite a growing body of evidence, advanced treatment options remain limited. However, with continued advances in therapy, quality of life and life expectancy will continue to improve.

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