Pulmonary Hypertension in Sickle Cell Disease

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Abstract: Pulmonary hypertension (PH), a disorder characterized by elevated pulmonary artery pressure and pulmonary vascular resistance, is an increasingly recognized complication of sickle cell disease (SCD), with a prevalence of approximately 30% in adult patients. It confers a high risk of death, with 2-year mortality rates of 40–50%, even at modest elevations of pulmonary pressures. The pathogenesis of PH complicating SCD is probably heterogeneous, including hemolysis and its effect on nitric oxide bioavailability, asplenia, thrombosis, chronic lung disease, and iron overload. Clinical manifestations of PH are difficult to recognize in sickle cell patients as they overlap with signs and symptoms of chronic anemia. Doppler echocardiography is recommended for screening, using tricuspid regurgitant jet velocity (TRV) to estimate pulmonary artery systolic pressure, with PH defined as TRV of at least 2.5 m/s. Detection of an elevated TRV is followed by characterization of PH by various tests to confirm diagnosis, define hemodynamics, identify underlying causes or associated diseases, determine severity and prognosis, and select appropriate therapy. Current data on treatment of PH in SCD are limited. Recommendations include intensification of sickle cell–directed therapies, treatment of causal factors or associated diseases, general supportive measures, and use of PH-specific pharmacologic agents. Further knowledge of the pathobiology of this complication and clinical trials of effective therapy are needed to improve survival.

Sickle cell disease (SCD) affects millions of people worldwide. In the United States, one of every 500 African Americans and one of every 1,000–1,400 Hispanic Americans are born with SCD, giving an estimate of about 72,000 people afflicted with the disease.[1] Prior to the 1970s, mortality among individuals with SCD was high and few patients reached adulthood, with an estimated median survival of 14 years.[2] Survival rates have improved over the last three decades due to advances in the management of SCD such as universal newborn screening, administration of prophylactic antibiotics, immunization for the prevention of life-threatening bacterial infections, hydroxyurea prophylaxis, and stroke prevention with chronic transfusions.[3] The Cooperative Study of Sickle Cell Disease, a longitudinal study of 3,794 patients from 1978 to 1988, reported that the median life expectancy for men and women

with hemoglobin SS was 42 and 48 years, respectively, and for men and women with hemoglobin SC was 60 and 68 years, respectively.[4] A more recent survival estimate from the Dallas Newborn Cohort predicted the cumulative overall survival of children with hemoglobin SS and sickle-β° thalassemia at 18 years of age to be 86%.[5] As more children with SCD survive into adulthood, hematologists caring for this patient population are faced with a new challenge of recognizing and treating the long-term complications of the disease.

Pulmonary complications, both acute and chronic, are the leading causes of morbidity and mortality in SCD.[4,6,7] Pulmonary manifestations in SCD include acute chest syndrome, airway obstruction, restrictive lung disease, oxyhemoglobin desaturation, thromboembolism, and chronic lung disease, which in its most severe form ultimately leads to pulmonary hypertension (PH).[6,8-10] Although underrecognized in the past, PH has emerged as an important complication and risk factor for death in adult sickle cell patients.[11]

This review highlights the epidemiology, pathogenesis, clinical presentation, diagnosis, and management of PH in patients with SCD.

Epidemiology

Pulmonary hypertension occurs frequently in adult patients with SCD. Researchers examining the lungs of 20 adult patients with SCD who died from various causes observed histologic changes diagnostic of grades I–IV PH in all 20 cases.[12] Sixty percent of these patients had plexiform lesions consistent with irreversible PH. Retrospective studies have shown that 20–40% of adult sickle cell patients screened with echocardiography have evidence of PH.[13,14] Similar findings were observed in recent prospective studies. Ataga and colleagues found that 18 of 60 (30%) adult patients 18 years or older followed at their sickle cell clinic had PH.[15] In the National Institutes of Health (NIH) sickle cell PH screening study, a prospective study of 195 adult sickle cell patients who were screened with transthoracic Doppler echocardiography using tricuspid regurgitant jet velocity (TRV) to estimate pulmonary artery systolic pressure, 32% of patients were found to have PH (defined as TRV ≥2.5 m/s), with 9% having moderate to severe PH (TRV ≥3 m/s).[11] The prevalence of PH was similar in men and women. Hemoglobin SC genotype was associated with a lower TRV, whereas increasing age was a predictor of a high TRV. Less is known about the prevalence of PH in the pediatric population. In retrospective single-institution reports using echocardiogram, PH was observed in 16–31% of children and adolescents, suggesting that PH may begin to develop in childhood.[16-19,70]

PH confers a high risk of mortality in sickle cell patients. In the NIH sickle cell PH screening study, Gladwin and coworkers[11] showed that a TRV of 2.5 m/s or greater is an independent risk factor for death as compared with a velocity less than 2.5 m/s. Patients with PH had an 18-month mortality rate of 16% compared with less than 2% for those without PH. Further follow-up of this cohort showed a 40-month mortality rate of 40% (relative risk 7.4; 95% confidence interval, 2.4–22.6; $P<.001$).[20] This finding confirms previously reported high death rates in patients with PH, with 2-year mortality rates of 40–50%.[6,14,21] This high risk of death occurs despite milder elevation of pulmonary artery pressure, lower pulmonary vascular resistance, and higher cardiac output than is observed in patients with idiopathic pulmonary arterial hypertension (PAH) or other forms of secondary PAH. Whether this high risk of death implicates elevated pulmonary pressures as a direct cause of death or a risk factor for multiorgan disease and generalized sickle cell vasculopathy is unclear.

Pathogenesis

The mechanism of PH complicating SCD is unknown and probably heterogeneous (Figure 1).

Chronic Hemolysis

Apart from vaso-occlusion, central to the pathophysiology and clinical manifestations of SCD is chronic hemolytic anemia. The development of PH in several chronic hemolytic disorders such as thalassemia, hereditary spherocytosis, and paroxysmal nocturnal hemoglobinuria suggests a mechanistic link between hemolysis and sickle cell–related PH. A novel mechanism of the clinical sequelae of hemolysis and its effect on nitric oxide (NO) biology has been proposed.[22] Cell-free plasma hemoglobin released during intravascular hemolysis leads to scavenging of NO.[23] In addition, hemolysis releases red cell arginase which degrades arginine, the substrate for endothelial NO synthase, resulting in decreased NO production.[24] The NO pathway is one of the major pathways known to be perturbed in patients with PAH. NO is a potent vasodilator and plays an important role in vascular endothelial homeostasis. Its depletion leads to vasoconstriction, endothelial dysfunction, platelet activation, oxidative stress, and proliferative vasculopathy that can ultimately lead to PH in SCD and other hemolytic anemias.[22,25] A recent study by Hsu and associates elegantly provides more evidence for a hemolysis mechanism due to global dysregulation of the NO pathway by demonstrating development of PH in sickle cell mice and a nonsickle mouse model of acute alloimmune hemolysis.[71] Another important mechanistic pathway known to be involved in

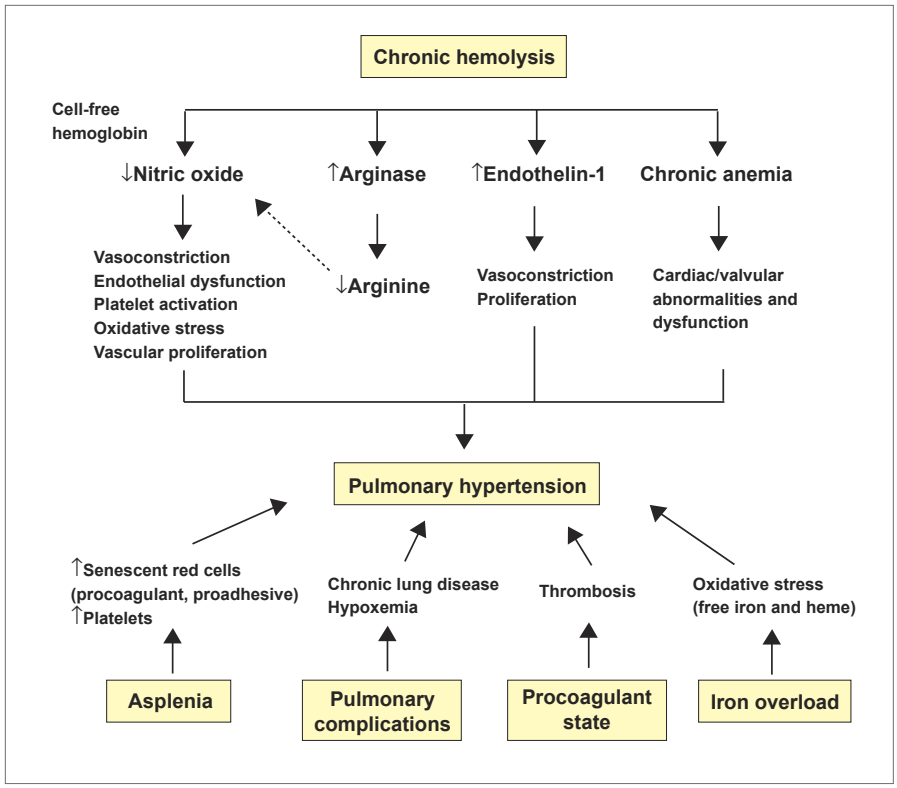

Figure 1. Potential mechanisms for the development of pulmonary hypertension associated with sickle cell disease.

the pathogenesis of PAH, the endothelin pathway, is also shown to be deranged in SCD. Endothelin-1 promotes pulmonary artery smooth muscle contraction, proliferation, and hypertrophy. Endothelin-1 is overexpressed in SCD,[26,27] potentially causing the development of sickle-related PH. It is also possible that the chronic anemia and hypoxemia caused by hemolysis may lead to cardiac and valvular abnormalities and dysfunction contributing to the pathogenesis of PH.[28]

Asplenia

Another factor that has been postulated to cause PH in chronic hemolytic disorders is asplenia. Sickle cell patients have functional asplenia and many patients with thalassemia and spherocytosis have had splenectomy. Asplenia increases platelets and platelet-derived mediators in the circulation as well as senescent erythrocytes that are highly proadhesive and procoagulant, inducing erythrocyte adhesion to endothelium and microvascular thrombosis.

Procoagulant State

Thrombosis is a known etiology of PH, with in situ thrombosis frequently seen in histopathologic specimens of PH patients. A procoagulant state exists in SCD that could promote development of thrombosis, including increased thrombin generation, deficiency of anticoagulant proteins, and abnormal activation of the fibrinolytic system.[29] Autopsy reports in sickle cell patients have shown pulmonary thromboembolism and features of progressive endothelial damage with concentric pulmonary vascular intimal hyperplasia and in situ thrombosis similar to those seen in patients with other forms of PH.[30,31]

Chronic Lung Disease and Nocturnal Hypoxemia

The frequent occurrence of pulmonary complications in SCD could also lead to PH. Recurrent acute chest syndromes secondary to infection, fat embolism, reactive airways, or hypoxemia can cause lung parenchymal and vascular injury that may eventually result in chronic lung disease and cor pulmonale in later stages.[6] Nocturnal hypoxemia, a well-known cause of PH, is well-described in the sickle cell population.[32,33] It may result from obstructive sleep apnea, abnormal oxyhemoglobin affinity, or lung disease, and has been linked to the development of stroke and painful crises.[33-35]

Iron Overload

In the NIH PH screening study, iron overload was found to be a risk factor for PH.[11] Neumayr and associates reported that transfused and less-chelated sickle cell patients have a higher rate of PH compared with nontransfused patients.[36] These observations suggest the possibility that iron toxicity may play a role in the pathophysiology of PH.

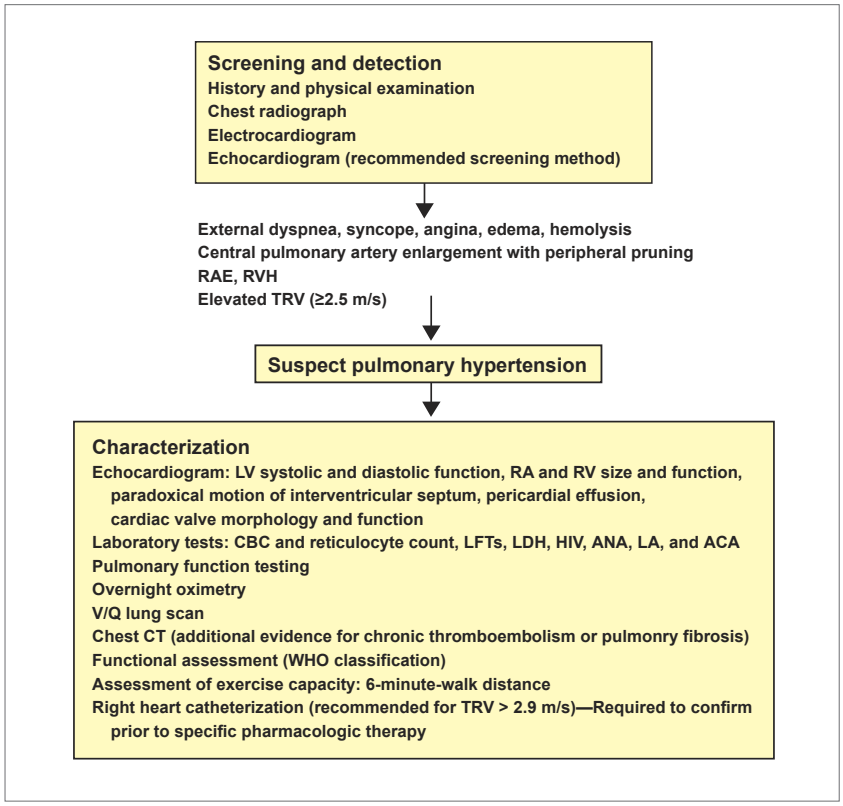

Figure 2. Diagnostic algorithm for the evaluation of pulmonary hypertension associated with sickle cell disease.

ACA=anticardiolipin antibody; ANA=antinuclear antibody; CBC=complete blood count; CT=computerized tomography; HIV=human immunodeficiency virus; LA=lupus anticoagulant; LDH=lactate dehydrogenase; LFTs=liver function tests; LV=left ventricle; RA=right atrium; RAE=right atrial enlargement; RV=right ventricle; RVH=right ventricular enlargement; TRV=tricuspid regurgitant velocity; V/Q=ventilation perfusion; WHO=World Health Organization.

Clinical Presentation

The clinical manifestations of PH, such as exertional dyspnea and fatigue, are often difficult to recognize in sickle cell patients because of their similarity to the signs and symptoms of chronic anemia. Most sickle cell patients detected to have elevated pulmonary artery pressures by echocardiography screening are asymptomatic. The classic symptoms of syncope, angina, and edema seen in advanced PH are not usually seen in these patients.

Several clinical and laboratory features may be helpful in identifying patients at risk for PH. Gladwin and his group have shown that manifestations of high hemolytic rate such as low hemoglobin, high lactate dehydrogenase (LDH), high aspartate transaminase, and high indirect bilirubin were correlated with PH, lending credence to the significance of hemolysis-associated NO depletion in the pathogenesis of PH.[11,37] Other clinical risk factors associated with PH are elevated systolic blood pressure, renal insufficiency, leg ulceration, priapism in males, older age, SS genotype, and possibly ischemic stroke.[11,15,37-39] Frequent acute chest syndromes, hydroxyurea use, and elevated levels of fetal hemoglobin, white blood cells, and platelets have not been consistently found to be related to PH.[11,15,40]

Echocardiography and cardiac catheterization data show that PH associated with SCD has features that are distinct from other forms of PH.[11,20,21,41] Sickle cell patients have a high baseline cardiac output (>8 L/min) due to high stroke volume necessary to compensate for chronic anemia. This results in a relatively lower pulmonary vascular resistance compared with that seen in other forms of PH (184±26 dyn · s/cm^5 vs 500–1,000 dyn · s/cm^5). In addition, patients with SCD frequently demonstrate high pulmonary capillary wedge pressure (17 mm Hg), which may indicate involvement of left heart disease in the pathogenesis of PH in certain patients.[41,42] Although pulmonary artery pressure is not usually as high as seen in other forms of PH (30–40 mm Hg vs 50–60 mm Hg), there may be a substantial reduction in functional capacity[43] and association with significant mortality.[11] Finally, pulmonary pressures can become significantly elevated during vaso-occlusive crises or exercise[44]; it is possible that sudden deaths that occur in sickle cell patients may be the result of sudden cardiac failure and dysrhythmias from acute rise in pulmonary pressures and limited cardiac reserve.

Diagnostic Evaluation

Screening and Detection

The high prevalence and association with high mortality of PH in SCD (even in milder forms without symptoms) justify routine screening of this patient population,

particularly in adults (Figure 2). Patients are often not sufficiently symptomatic, nor with any specific physical signs of PH. Although certain signs on chest radiograph (central pulmonary artery enlargement with peripheral pruning of pulmonary vasculature and right ventricular enlargement) and electrocardiogram (right ventricular strain pattern) may indicate the presence of PAH, these tests are relatively insensitive and nonspecific. The recommended method for screening is transthoracic Doppler echocardiography, which provides a reliable noninvasive estimation of pulmonary artery systolic pressure that correlates with invasively measured pulmonary artery pressure.[45] It is derived from calculation of the TRV using the modified Bernoulli equation: [pulmonary artery systolic pressure = ($4 \times TRV^2$) + right atrial pressure estimate]. Right atrial pressure is either a standardized value (5–15 mm Hg) or an estimated value from the characteristics of the jugular venous distension.

By expert consensus, PH is defined as pulmonary artery systolic pressure greater than 35 mm Hg or mean pulmonary artery pressure greater than 25 mm Hg at rest or greater than 30 mm Hg during exercise. To avoid the subjective estimation of right atrial pressure, Gladwin and colleagues[11] used a simplified definition of PH by a specific TRV of at least 2.5 m/s in their prospective screening study of adult sickle cell patients and found this cut-off value to be associated with high risk of death. A TRV of at least 3 m/s was used to define moderate-to-severe PH.

There is no consensus as to the frequency of assessment and target age group for screening. Recommendations for periodic screening in adults vary from every 2 to every 5 years.[41,46] Data in the pediatric population are too limited to make any recommendations. Practice guidelines in pediatrics have suggested performing echocardiography as part of the baseline evaluation in patients 2 years or older, particularly in those with severe and frequent acute chest syndromes or unexplained cardiopulmonary symptoms.[47,48] Although specific assessments were not indicated in these guidelines, evidence for PH should be part of routine echocardiographic evaluation. Any patient at any age with symptoms suggestive of PH such as dyspnea on exertion, syncope, angina, and edema warrants an evaluation for detection of PH. Moreover, patients with evidence of high hemolytic rate (low hemoglobin levels, elevated values for reticulocytes, indirect bilirubin, aspartate transaminase, and/or LDH), systemic hypertension, renal insufficiency, priapism, or leg ulceration should also be selected for PH screening, given the strong association of these markers with the diagnosis of PH.

As previously mentioned, pulmonary pressures have been observed to significantly increase in the setting of sickle cell crisis, such as pain or acute chest syndrome as well as during exercise. Therefore, screening must be performed at rest during steady-state, at least 2 weeks after an acute painful crisis and 4 weeks after an acute chest syndrome or blood transfusion.[41]

Characterization

Following detection of an elevated TRV by echocardiography, characterization of PH is essential to confirm the diagnosis, define specific hemodynamics, identify underlying causes or associated diseases, determine severity and prognosis, and select appropriate therapy.[49,50]

Doppler Echocardiography A repeat echocardiography to document a consistently elevated TRV is recommended, as variations in TRV have been observed on follow-up studies, particularly in those with mild TRV elevations.[46] In addition to providing an estimate of pulmonary artery systolic pressure derived from TRV, echocardiography also provides essential information, including left ventricular systolic and diastolic function, right atrial size, right ventricular size and function, paradoxical motion of the interventricular septum, presence of pericardial effusion, and morphology and function of all cardiac valves.

Laboratory Tests These should include tests to evaluate for causal factors or diseases associated with PH, including complete blood count with reticulocyte count, liver function tests, serum LDH, HIV testing, antinuclear antibody to screen for connective tissue disorder, and antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibodies).

Pulmonary Function Testing and Overnight Oximetry Pulmonary function testing (spirometry, lung volumes, and diffusion capacity) is indicated to assess the contribution of airway obstruction and parenchymal disease, which are not uncommon in the sickle cell population. Overnight oximetry is performed to screen for nocturnal hypoxemia and exclude causes like obstructive sleep apnea.

Radiographic Studies Ventilation/perfusion lung scintigraphy is used to diagnose chronic thromboembolic PH that may be seen in sickle cell patients particularly because of their underlying procoagulant state. Chest computerized tomography may be required to provide additional evidence for chronic pulmonary embolism or other underlying lung disease such as pulmonary fibrosis.

Functional Assessment and Exercise Capacity Evaluation of symptoms by the World Health Organization classification of functional status (Table 1) and assessment of exercise capacity are important prognostic indicators in PH and are used to evaluate response to therapy. The most commonly used exercise test is the 6-minute-walk distance

Table 1. World Health Organization Classification of Functional Status of Patients With Pulmonary Hypertension

Class I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II	Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less-than-ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class IV	Patients with pulmonary hypertension resulting in the inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present at rest, and discomfort is increased by any physical activity.

(6MWD), which measures the distance an individual can walk at an unhurried pace. It is fairly simple and can be performed in ambulatory settings. It correlates inversely with functional status severity and directly with baseline cardiac output and total pulmonary resistance, peak exercise oxygen consumption, peak oxygen pulse, and minute-ventilation-carbon dioxide output slope in idiopathic PH.[49] Preliminary data in sickle cell patients showed that the 6MWD is an adequate measure of functional capacity and response to therapy in this population. It correlated directly with peak oxygen consumption and inversely with mean pulmonary artery pressure and TRV.[43]

Right Heart Catheterization Right heart catheterization is required to confirm the diagnosis of PH. It provides hemodymanic measurements to characterize etiology, severity, and prognosis of PH, including cardiac output, pulmonary vascular resistance, and pulmonary capillary wedge pressure, which is essential for exclusion of left heart disease or pulmonary vein obstruction. The hemodynamic definition of PAH is mean pulmonary artery pressure greater than or equal to 25 mm Hg, with pulmonary capillary wedge pressure less than 15 mm Hg and pulmonary vascular resistance of greater than 3 Wood units. In sickle cell patients in which certain unique characteristics of PH are noted indicating the presence of left heart disease (increased pulmonary capillary wedge pressure), it is particularly important to perform cardiac catheterization before initiating PH-specific pharmacologic therapy.

A vasodilator study is also conventionally performed in patients with idiopathic PAH to detect either beneficial or detrimental effects of acute treatment with short-acting vasodilators (intravenous epoprostenol, intravenous adenosine, or inhaled NO) to predict which patients may benefit from long-term calcium channel blockers. However, with the new oral and inhaled vasodilatory and antiproliferative agents now available for treatment of PH, the utility of performing the vasodilator challenge test is less clear, including in the sickle cell population in which calcium-channel blockers are rarely used.[20,49]

Management

Current data regarding management of PH related to SCD are limited to anecdotal experience, expert opinion, and small clinical studies. Options include intensification of sickle cell–directed therapies, treatment of causal factors or associated diseases, general supportive measures, and use of PH-specific pharmacologic agents (Figure 3).

Sickle Cell–Directed Therapies

Conventional treatments used for other sickle cell complications such as hydroxyurea and chronic red-cell transfusions are recommended as first-line and probably also as mainstay therapy of PH associated with SCD.[20,41] These are aimed at reducing hemolysis, improving anemia and oxygen delivery to enhance cardiopulmonary function, and preventing end-organ damage and acute sickle cell complications that could aggravate PH.

Hydroxyurea has been shown to reduce painful events and acute chest syndromes and improve survival in sickle cell patients.[7,51,52] Although the exact mechanisms of action remain uncertain, the therapeutic efficacy of hydroxyurea is attributed to induction of fetal hemoglobin and potentially to reduction of white blood cell and platelet counts, improved rheology, and decreased endothelial red blood cell adhesion.[53] Several investigators have also demonstrated an interesting relationship between hydroxyurea and NO, including reports that hydroxyurea increases the levels of NO and that NO plays a role in hydroxyurea induction of fetal hemoglobin.[54-56] Given the critical role of NO depletion in the pathogenesis of PH, these observations may support an important role for hydroxyurea in the treatment of PH in SCD, although epidemiologic data from the NIH sickle cell PH screening study did not show an association between the use of hydroxyurea and the prevention of the development of PH.[11]

Long-term transfusion with maintenance of hemoglobin S concentration at <30–50% has been shown to

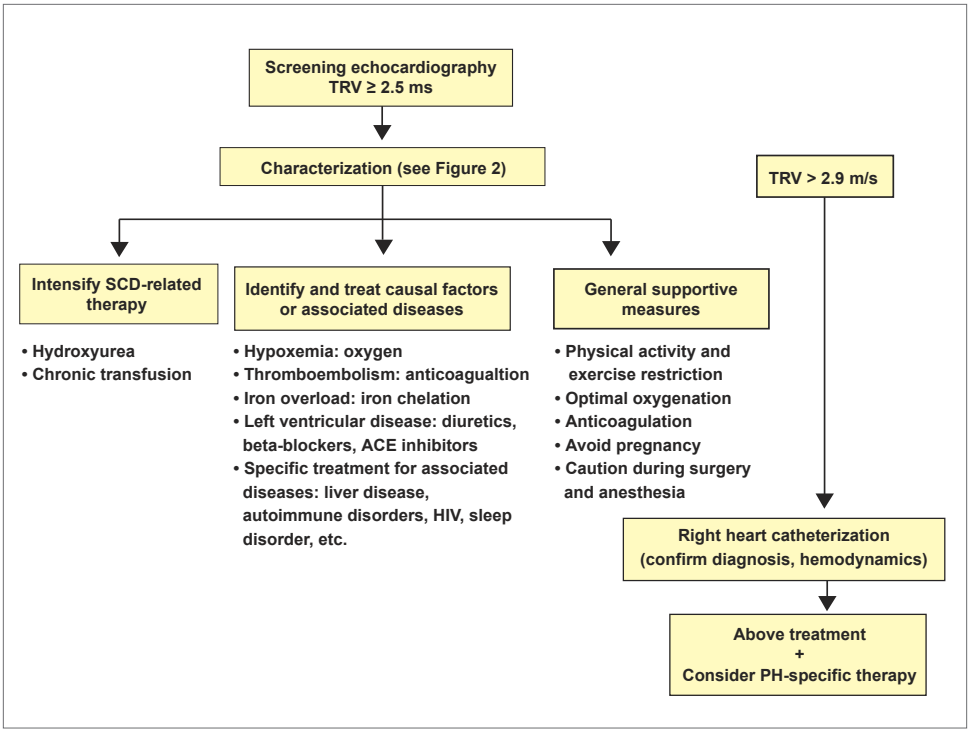

Figure 3. Treatment algorithm for pulmonary hypertension associated with sickle cell disease.

ACE=angiotensin converting enzyme; PH=pulmonary hypertension; SCD=sickle cell disease; TRV=tricuspid regurgitant velocity.

diminish the risk of cerebrovascular and other sickle cell complications.[57,58] Children receiving chronic transfusions for prevention of stroke were observed to have a lower incidence of acute chest syndromes and painful events and improvement in growth and development.[59,60] It has also been observed that laboratory parameters associated with hemolysis and endothelial adhesions improve with transfusions.[61,62] These beneficial effects from chronic transfusions justify their use for treatment of PH in these patients. Unfortunately, long-term transfusion is inevitably accompanied by iron overload, which in itself is a probable contributor to the development of PH. As such, iron chelation must be implemented along with chronic transfusions.

Treatment of Causal Factors or Associated Diseases

Vigorous search for and treatment of other underlying pathologies associated with PH such as chronic lung disease, hypoxemia, thromboembolism, HIV, liver disease, autoimmune disorders, and iron overload must be employed to prevent further progression of PH. For instance, hypoxemia causes pulmonary vasoconstriction leading to increased pulmonary pressures; thus, oxygen supplementation is recommended for patients with hypoxemia from various causes such as chronic lung disease or nocturnal hypoxemia. Anticoagulation has been shown to improve survival in idiopathic PAH[63,64]; however, its use for other forms of PH is controversial. In the absence of any contraindication, such as risk for hemorrhagic stroke, it may be reasonable to place sickle cell patients with PH on warfarin given their inherent hypercoagulable state. Iron chelation is indicated for patients who are on chronic transfusion therapy as well as those who show evidence of increased iron burden from multiple episodic transfusions.

General Supportive Measures

Cautious use of diuretics is indicated to treat volume overload in patients with evidence of heart failure. The role of cardiac glycosides (digoxin) is unclear, although some experts administer digoxin for right ventricular failure or low cardiac output. Supplemental oxygen to maintain oxygen saturation above 90% is recommended under conditions that could induce hypoxia such as exposure to high altitudes or during air travel. Certain restrictions to physical activity and exercise are usually recommended for patients with PH. Heavy physical activity and isotonic exercise that can induce exertional syncope are discouraged, but low-grade aerobic exercise such as walking as tolerated is allowed. Pregnancy poses a high risk for mortality in PH patients[65] and most experts recommend avoidance or early termination of pregnancy in women with PH.[66] This recommendation should apply as well to women with SCD and PH. Careful evaluation of the benefits of elective surgery is indicated to avoid the risks of hemodynamic and ventilatory compromise with surgery and anesthesia.

PH-specific Pharmacologic Treatments

At present, three major classes of pharmacologic agents

Table 2. Pharmacologic Agents Approved for Use in Pulmonary Arterial Hypertension

Class	Drug	Mechanisms of Action	Route	Doses	Common Side Effects	Concerns in Sickle Cell Disease
Prostanoids	Epoprostenol	Potent short-acting vasodilator; antiproliferative; antithrombotic	cIV	Broad dosing range; Average 40 ng/kg/min	Flushing, headache, jaw pain, nausea, diarrhea, arthralgias, IV line infection and thrombosis	Systemic vasodilation and ↑ cardiac output → high output failure, line infection and thrombosis
	Treprostinil	Short-acting vasodilator; antiproliferative; antithrombotic	SC, cIV	Broad dosing range; doses required are higher than for epoprostenol	SC infusion site pain and reaction, IV line infection and thrombosis, headache, diarrhea, nausea, rash	High output failure, infusion site reaction, line infection and thrombosis
	Iloprost	Short-acting vasodilator; antiproliferative; antithrombotic	INH, IV	2.5–5.0 µg/INH 6–9 times/day	Flushing, headache, diarrhea, nausea, jaw pain, cough, edema	High output failure (uncertain)
Endothelin receptor antagonist	Bosentan	ET_A and ET_B receptor antagonist	PO	125 mg TID	Hepatotoxicity, flushing, headache, anemia	Hepatotoxicity, anemia
PDE-5 inhibitor	Sildenafil	Inhibition of deactivation of cGMP (intracellular secondary messenger that mediates the vasodilatory activity of NO)	PO	20 mg TID	Headache, dyspepsia, sinus congestion, epistaxis, hypotension	May induce priapism (males)

cGMP=cyclic guanosine monophosphate; cIV=continuous IV infusion; ET=endothelin; INH=inhalation; IV=intravenous; NO=nitric oxide; PDE-5=phosphodiesterase-5; PO=oral; SC=subcutaneous.

are available for the treatment of PAH: prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 (PDE-5) inhibitors.[67] Table 2 summarizes the important features of these agents, including concerns for their use in SCD. Selection of PH-targeted treatment is complicated and experience in SCD is very limited. Bosentan (Tracleer, Actelion), an orally administered dual endothelin A and B receptor antagonist that is approved for the treatment of moderate to severe PAH, is presently being assessed in a double-blind, placebo-controlled study in SCD. A promising NO-based pharmacologic agent for use in sickle cell patients is sildenafil (Viagra, Pfizer), a PDE-5 inhibitor that prevents the deactivation of cyclic guanosine monophosphate, a secondary messenger of NO-dependent signaling. Because PDE-5 levels are high in the pulmonary vasculature as well as in the corpora cavernosa, priapism as a side effect in male sickle cell patients is a concern. Preliminary data in SCD suggest that sildenafil caused a significant decrease in TRV and improvement in exercise capacity (6MWD). No priapism was observed in 3 male patients.[68] L-arginine, a nitrogen donor for the synthesis of NO by NO synthase, has also been shown to decrease pulmonary artery pressure in sickle cell patients with PH and is another potential NO-based agent for sickle cell–related PH.[69] Clinical trials using targeted PH treatment in sickle cell patients are ongoing, but whether any of these treatments will improve outcome for PH in sickle cell patients remains unknown.

Future Directions and Conclusions

PH is an important complication of SCD. It confers a significant risk of death, particularly in adults, even at modest elevations of pulmonary pressures. Screening with Doppler echocardiography is warranted to enable early treatment and prevent progression and mortality. Further knowledge of the pathobiology of this complication in relation to hemoglobinopathies, and large-

scale clinical trials of effective therapy, are needed to improve survival.

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(Continued on page 585)

(Lee, Rosenzweig, and Cairo, continued from page 653)

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