Concise Clinical Review

Pulmonary Complications of Sickle Cell Disease

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Sickle cell disease (SCD) is a common monogenetic disorder with high associated morbidity and mortality. The pulmonary complications of SCD are of particular importance, as acute chest syndrome and pulmonary hypertension have the highest associated mortality rates within this population. This article reviews the pathophysiology, diagnosis, and treatment of clinically significant pulmonary manifestations of SCD, including acute chest syndrome, asthma, and pulmonary hypertension in adult and pediatric patients. Clinicians should be vigilant in screening and treating such comorbidities to improve patient outcomes.

Keywords: sickle cell disease; hemolytic anemia; pulmonary hypertension; sudden death; nitric oxide

Sickle cell disease (SCD) is an autosomal recessively inherited genetic disorder caused by a single point mutation in the gene encoding the β-globin chain of hemoglobin (1, 2). It is one of the most common monogenetic disorders in the world, affecting nearly 1 in 600 African Americans (3) and an estimated 1 to 4% of babies born in sub-Saharan Africa (4). The resulting hemolytic anemia is most severe in patients homozygous for the sickle hemoglobin (HbS) gene mutation (Hb-β; glu6val). The intensity of hemolytic anemia is less severe in individuals with concurrent α-thalassemia (homozygous or heterozygous for a single α-globin gene [HbA1, HbA2] deletion), a genotype found in one-third of individuals with sickle cell anemia; however, rates of vasoocclusive pain crisis (VOC) and acute chest syndrome (ACS) increase. Anemia is least severe in patients with HbSC disease (compound heterozygosity for HbS and HbC [HBB; glu6lys]), who suffer from increased complications arising for vasoocclusion coupled to high blood viscosity, such as retinal disease and avascular necrosis of the femoral head (1, 3, 5).

Hemoglobin S polymerizes on deoxygenation, inducing erythrocyte distortion, rigidity, and membrane structural damage. These changes alter cellular rheologic properties, enhance adhesion molecule expression, impair microvasculature blood flow, and promote hemolysis and vasoocclusive episodes (3). The degree of polymerization primarily determines illness severity (6) and is proportional to the degree and duration of deoxygenation and the intracellular HbS concentration raised to approximately the 15th to 34th power (2, 3, 7).

The complications of SCD are myriad. The two most common acute events are VOC and ACS, a lung injury syndrome (8, 9). Additionally, patients are at risk for a progressive vasculopathy characterized by systemic and pulmonary hypertension (PH), endothelial dysfunction, and proliferative changes in the intima and smooth muscle of blood vessels (1, 3, 10, 11). With increasing age, the incidence of chronic end-organ complications, including chronic renal failure, osteonecrosis, and PH, increases. The pulmonary complications of SCD are of particular importance, as ACS and PH have the highest associated mortality rates within this population (8, 9, 11, 12). This article reviews the pathophysiology, diagnosis, and treatment of clinically significant pulmonary manifestations of SCD, including ACS, restrictive lung disease, asthma, and PH in adult and pediatric patients.

ACUTE CHEST SYNDROME

ACS is an acute lung injury syndrome that occurs frequently in patients with SCD. This lung injury syndrome has been defined in clinical research studies as a new pulmonary infiltrate on chest X-ray consistent with alveolar consolidation but not atelectasis, involving at least one complete lung segment. The radiographic abnormality is usually accompanied by one or more new signs or symptoms, including chest pain, fever, tachypnea, wheezing, cough, or hypoxemia (3, 5, 9). Although usually self-limited, some episodes progress rapidly to acute respiratory failure causing substantial morbidity and death (13). ACS is the second most common reason for hospitalization after VOC (14, 15). In the Cooperative Study of Sickle Cell Disease, a 29% incidence of ACS was reported in 3,751 subjects over a 2-year period, representing 12.8 episodes per 100 patient-years for HbSS disease (16). Before the recognition of PH, ACS was considered the leading cause of premature death, accounting for 25% of sickle cell–related mortality in early registry trials (8, 15–17). The associated mortality has decreased in the modern era of hydroxyurea therapy and early, more aggressive transfusion therapy (18). More commonly, ACS-associated mortality is related to underlying PH and acute cor pulmonale, which may provide a two-hit event that destabilizes the patient (19).

ACS occurs in 10 to 20% of hospitalized patients with SCD, usually 1 to 3 days after admission for severe VOC (9, 18), whereas in children it often presents as an admitting diagnosis. These differences may be explained by the higher prevalence of fat emboli syndrome in adults and community-acquired atypical or viral infections in children (9, 16). Risk factors for increased ACS frequency include younger age, higher steady-state hemoglobin

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level, lower hemoglobin F concentrations, higher steady-state leukocyte counts, history of asthma (in children) (20), active smoking, or environmental smoke exposure (21) and may be more severe in individuals with HbSS as compared with HbSC disease (5, 9, 15, 20, 22–25).

The etiology of ACS is multifactorial. The three primary studied mechanisms include pneumonia or systemic infection, fat embolism, and direct pulmonary infarction from HbS-containing erythrocytes (3, 9). The National ACS Study Group (671 ACS episodes in 538 patients) identified an infectious agent (mostly atypical bacteria or viruses) in 54% of ACS admissions (Figure 1) (9). Community-acquired encapsulated bacteria were isolated in less than 10% of cases, despite the fact that most patients with HbSS have functional asplenism. Additionally, methicillin-resistant *Staphylococcus aureus* has been observed late in the hospital course in patients with severe ACS, especially in patients with large pleural effusions (9). Moreover, severe ACS related to seasonal influenza, including H1N1, has also been described (26–28).

It has been proposed that community-acquired respiratory infection induces an excessive inflammatory lung injury response in the susceptible patient with SCD. Consequently, more than 80% of adult patients with SCD report a history of hospitalization with "pneumonia" requiring intravenous antibiotics (11). Transgenic mouse models of SCD that express only human HbS suggest increased susceptibility to inflammatory triggers (lipopolysaccharide and bacteria) and development of lung injury at lower endotoxin levels that do not adversely affect wild-type mice (29, 30).

Fat emboli syndrome represents another major ACS etiology. Severe VOC involving multiple bones, especially the pelvis and femur, results in infarction and edema of the marrow compartment (3). The marrow undergoes necrosis, and its contents, including fat, cells, and even bony spicules, access the bloodstream and are carried to the lung. After lodging in the lung vasculature, direct cellular occlusion and secondary inflammatory events lead to acute hypoxemia and PH (31–33). This syndrome should be suspected in patients with abrupt multiorgan failure with rapid development of the acute respiratory distress syndrome, acute increases in pulmonary arterial pressures, evidence of hepatopathy, alterations in mental status, prominent thrombocytopenia, and/or coagulopathy (34, 35). The identification of oil-red-O–positive lipid accumulations within alveolar macrophages is diagnostic of fat emboli to the lung and has been associated with systemic fat emboli syndrome (9, 33). The National ACS Study Group identified fat emboli syndrome in 16% of ACS cases in adults and children based on positive lipid accumulations in alveolar macrophages obtained by bronchoscopy (9). One study compared induced sputum sampling of alveolar macrophages with samples obtained from bronchoalveolar lavage and found a modest but significant correlation ($R = 0.65$) (33). In this study, patients with induced sputum lipid-laden macrophages had significantly more extrathoracic pain, more neurological symptoms, a lower platelet count, and higher hepatic transaminase levels than those without evidence of fat emboli, suggesting fat embolization–associated ACS may manifest a more severe course with systemic complications.

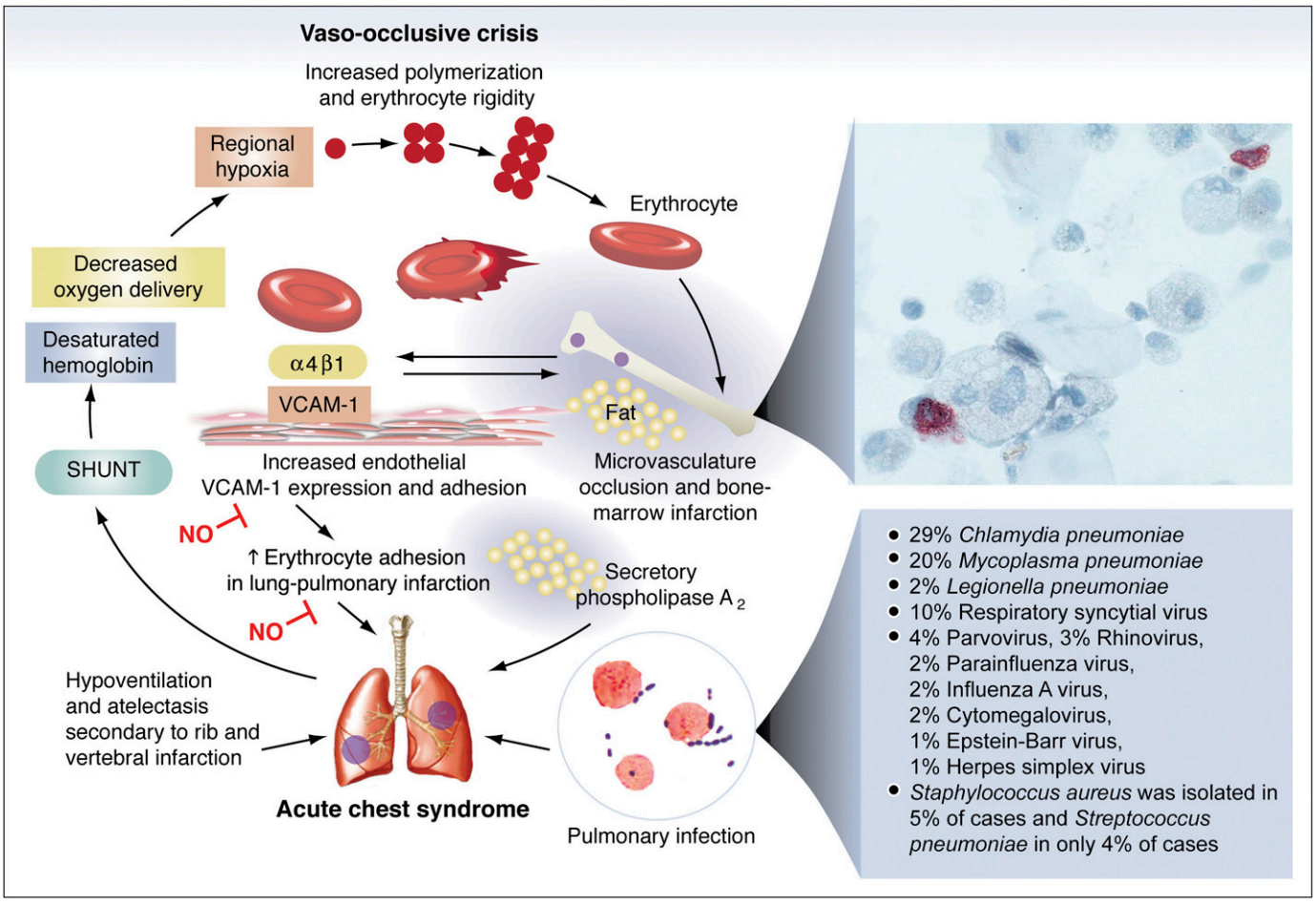

Figure 1. Vicious cycle of vasoocclusive crisis and acute chest syndrome. Modified by permission from Reference 3.

Direct adhesion of sickled cells in the pulmonary vasculature with vascular occlusion and infarction has been proposed as a third mechanism for ACS, but the exact prevalence of this mechanism is unknown. Rarely, overt lung infarction with cavitation is observed. A recent French study evaluated pulmonary artery thrombosis by CT–pulmonary angiography in 125 consecutive patients with 144 episodes of acute ACS. Surprisingly, investigators noted a 17% prevalence of subsegmental thromboembolism, without associated peripheral thrombosis, suggestive of *in situ* thrombosis or cellular occlusion (36). More work will be required to characterize this newly appreciated endophenotype of ACS (mechanisms of ACS are shown in Figure 1).

In terms of risk factors for developing ACS during VOC hospitalizations, it is notable that ACS is typically preceded by severe limb and chest pain and fevers. Although a high steady-state hemoglobin level is an independent ACS risk factor, it is often preceded by a fall in baseline hemoglobin (mean decrease of 0.78 g/dl) and rising lactate dehydrogenase levels. This suggests that steady-state high hemoglobin levels are a risk factor for VOC and ACS, likely related to viscosity effects of higher steady-state hemoglobin levels promoting vasoocclusive events, but after VOC develops, acute hemolysis may contribute to the development of lung injury. Similarly, preceding and during an ACS event, the platelet counts drop. Because functional asplenia typically manifests with baseline thrombocytosis in (approximately $400 \times 10^3/\mu l$), a drop below $200 \times 10^3/\mu l$ has been identified as an independent risk factor for multilobar ACS and mechanical ventilation (3, 9). The relationship between increased intravascular hemolysis and thrombocytopenia suggests a possible thrombotic thrombocytopenic purpura–like mechanism may occur in a subset of patients with ACS. Indeed, recent studies suggest that hemoglobin produced during hemolysis may inhibit ADAMTS13 activity (37–39). This remains an area of active basic investigation and could open the door to new therapeutic approaches for ACS.

A number of studies have suggested that acute increases in the blood levels of secretory phospholipase A2 (sPLA2) immediately predate and predict ACS development (32, 40). Activated sPLA2 converts marrow fat into inflammatory free fatty acids that cause lung injury. Based on these observations, a small study evaluated the efficacy of prophylactic blood transfusions in patients with sPLA2 elevation during VOC (41). This therapeutic approach eliminated ACS in this very small cohort, suggesting that larger confirmatory trials are indicated.

It is our practice to perform transthoracic echocardiography in patients admitted to the intensive care unit (ICU) for ACS for risk assessment and possible intensification of therapy. A prospective analysis of 70 consecutive adults (84 episodes) receiving standardized ICU treatment for ACS reported that both an elevated Doppler echocardiographic estimate of pulmonary artery systolic pressure, defined by a tricuspid regurgitant jet velocity (TRV) greater than or equal to 3 m/s, and right ventricular dilation and dysfunction (cor pulmonale) were frequent, occurring in 13% of cases (19). Pulmonary hypertension and right ventricular failure correlated with elevations in B-type natriuretic peptide levels, troponin I levels, invasive ventilation requirement, and mortality. Pulmonary hypertension in the setting of ACS was correlated to markers of more severe hemolysis and liver dysfunction (19). In our experience over the last 10 years at the National Institutes of Health, we have also observed that a subset of patients with VOC and ACS develop hyperhemolysis and thrombocytopenia, often associated with severe PH with right ventricular dilation and failure. It is our practice to move to more aggressive exchange transfusions in these patients and monitor them in the ICU setting.

ACS TREATMENT

Therapies reported to prevent ACS in at-risk patients include preoperative blood transfusion (42), maintenance asthma therapy for children with asthma (43), maintenance hydroxyurea therapy (14, 44), and the use of incentive spirometry during acute VOC hospitalizations (14, 17, 45).

Standard therapy during ACS events includes nonspecific supportive care strategies aimed at hastening recovery to baseline, including hospitalization, hydration, analgesics, broad-spectrum antibiotics (guided by regional resistance patterns and season, including coverage for atypical bacteria and seasonal influenza), incentive spirometry, supplemental oxygen, and blood transfusions (13, 14, 46).

Although there are no prospective studies demonstrating that transfusions, either exchange or simple, alter the outcome of ACS, transfusion in patients with ACS acutely increases hemoglobin oxygen saturation and has been shown to prevent ACS during major surgery (9, 42, 47). Analysis by the National ACS Study Group showed that the oxygenation significantly improved with transfusion. In patients who had hypoxia before transfusion (defined as an oxygen saturation $< 91\%$), the values increased from 86 to 93% ($P < 0.001$), and both simple and exchange transfusion resulted in similar improvements (9). It is now standard of care to initiate transfusion therapy for patients with ACS. In the recently completed DeNOVO trial, there were no patients mechanically ventilated and no deaths in 30 patients with ACS receiving the current practice of early transfusion therapy, suggesting improved outcomes compared with historical data from the National ACS Study Group, in which 13% of patients required mechanical ventilation (9, 18).

Simple packed red blood cell transfusions appear to be as effective as full exchange transfusion (9). To avoid excessively increasing blood viscosity, simple transfusion should be reserved for patients with hemoglobin values less than 10 g/dl. Because most patients with ACS drop their hemoglobin, it is usually feasible to transfuse two to four units in the first 24 hours and then maintain hemoglobin levels at 10 to 11 g/dl with subsequent transfusions. However, in severe or rapidly progressive illness, exchange transfusion is advised (48). It should be noted that one of the major iatrogenic complications in the treatment of ACS is transfusion of alloreactive blood. This often occurs because prior alloantibody levels become unmeasurable over time but are produced with repeat exposure. We recommend contacting other hospital blood banks where transfusions were delivered in the past to check for prior red cell antibodies. Additionally, routine partial matching for Rh antigens D, C, and E, as well as Kell can reduce this risk substantially (9, 49).

Corticosteroids as a treatment for ACS have been shown in three placebo-controlled trials to reduce length of hospitalization by 24 hours; however, this was associated with significant rebound VOC events necessitating rehospitalization in up to 25% of patients.

Concerns over side effects, including avascular necrosis, rebound VOC (50), and association with hemorrhagic stroke (51, 52), have limited enthusiasm regarding corticosteroid use in patients with SCD.

Noninvasive ventilation (NIV) has also been investigated as a means to alter patient outcomes in the setting of ACS. In a prospective randomized open single-center study of 67 adult patients with ACS in a French teaching hospital, NIV use improved respiratory rate and gas exchange; however, NIV failed to significantly reduce the number of patients remaining hypoxemic at Day 3 and was associated with greater patient discomfort (13). Additionally, NIV did not change transfusion rates, pain scores, narcotic dose,

or hospital length of stay, but instead prolonged length of stay in the step-down unit (13).

We have explored inhaled nitric oxide (NO) therapy for patients with SCD presenting in VOC in a relatively large placebo-controlled trial. Despite positive early small phase II trials (53, 54), we observed no effect of inhaled NO therapy on the duration of pain crisis, narcotic use, pain scores, or the development of ACS (18).

RESTRICTIVE LUNG DISEASE

Patients suffering from repetitive episodes of ACS can develop scattered areas of lung fibrosis, predominately observed in the lung bases. Figure 2 illustrates two examples of this lung fibrosis in adult patients with SCD. The development of advanced chronic lung disease in patients with SCD has been called sickle cell chronic lung disease (55). Although patients can present with advanced interstitial lung disease, as illustrated in Figure 2A, this is a relatively rare complication. High-resolution CT studies usually reveal a few scattered foci of lung scarring. In the historical SCD registry study, the Cooperative Study of Sickle Cell Disease, which was performed in the pre-hydroxyurea treatment era, pulmonary function studies were available for analysis in 310 patients with HbSS with SCD (56). Ninety percent of the population had abnormal pulmonary function studies, and the major abnormality was a mild restrictive pulmonary function defect (TLC of 70 ± 15% predicted) and isolated reduction in the D_{LCO} (57 ± 20% predicted). The spirometry was technically within the normal range, but the population means for FEV_1 (83% predicted) and FVC (84% predicted) were low–normal, with an FEV_1/FVC of 98% predicted. Obstructive disease, either alone or mixed with restrictive disease, was relatively uncommon in adult patients, occurring in 3% of the patients. Similar findings of mild restrictive abnormalities have been observed in more recent cohort studies of adult patients (57).

ASTHMA/REACTIVE AIRWAYS DISEASE

Asthma affects approximately 12% of all United States children (58), 15 to 20% of African American children, and 9% of African American adults (20, 58, 59). The prevalence of asthma among pediatric patients with SCD appears to be similar to that in children of African descent in the general population (57, 60). As mentioned earlier, obstructive lung disease in adults with SCD is less common, occurring in less than 3% of patients (56).

Based on asthma pathogenesis, ventilation–perfusion mismatching may result in local tissue hypoxia and increase red cell sickling. Supporting this concept, asthma has been associated with increased rates of ACS events in children (14, 15, 20, 23–25, 59, 61, 62). A retrospective case-control analysis of 139 pediatric patients admitted for VOC reported that patients with asthma were four times (95% confidence interval [CI], 1.7–9.5) more likely to develop ACS during the admission, had longer hospitalizations (5.6 vs. 2.6 d, $P = 0.01$), and had greater 72-hour readmission rates postdischarge (80 vs. 10%). Moreover, a subsequent prospective observational analysis of 291 patients with HbSS followed for 4,062 patient-years reported that pediatric patients with asthma suffered twice as many ACS episodes as patients without asthma (0.39 vs. 0.20 episodes per patient-year, $P < 0.001$). Pediatric patients with SCD with asthma develop a first ACS episode at a younger age, with a median age of 2.4 versus 4.6 years (hazard ratio, 1.64; 95% CI, 1.13–2.39; $P = 0.010$), and require more transfusions (1.00 vs. 0.60 per patient-year, $P = 0.02$) than patients without asthma (20); however, no significant difference in hospital length of stay or transfusion requirement per ACS episode are reported (20).

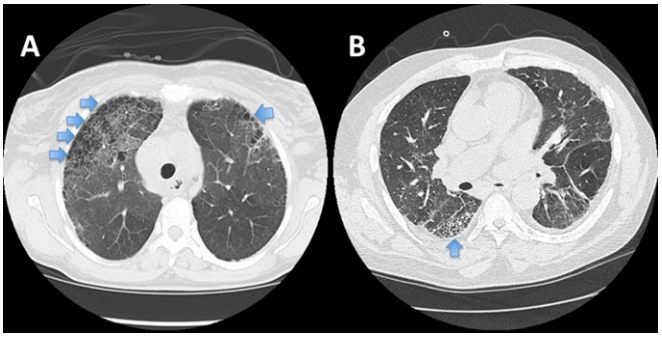

Figure 2. Radiographic evidence of pulmonary fibrosis related to multiple episodes of acute chest syndrome in two patients with sickle cell disease. Note the subpleural honeycombing fibrosis denoted by *arrows*.

Asthma is also associated with increased mortality in SCD (20, 59). For example, a study of 1,963 patients with SCD found that asthma was associated with twofold higher risk of all-cause mortality (59). The median life span for individuals with and without asthma who survived to age 5 years was 52.5 and 64.3 years of age, respectively (59). The reasons for increased mortality remain unclear.

The associated morbidity of asthma in adults with SCD is less clear and relatively understudied. A recent small cohort study evaluated physician-diagnosed asthma and a history of wheezing in 114 adults with SCD (63). Although self-reported severe and recurrent wheezing was associated with increased rates of pain, ACS, and risk of death, they found no relationship between a physician diagnosis of asthma and complications.

Asthma Treatment

Due to a lack of controlled trials in patients with SCD, little is known about the effects of asthma therapies in this population. Patients with asthma with SCD should be treated similarly to patients without SCD in accordance with National Institutes of Health (NIH) guidelines (58, 64). The primary concerns associated with short-term systemic corticosteroid use in patients with SCD presenting with severe asthma are rebound VOC events and theoretical concerns of arrhythmia associated with QT prolongation. Despite potential risks, corticosteroids should not be withheld from patients with SCD presenting with severe asthma, but close observation and early therapy for rebound VOC and ACS must be a standard for such intervention. Emergency department care should include oxygen, a short-acting β_2-agonist, and systemic corticosteroids for moderate or severe exacerbations. Magnesium sulfate may be considered for severe cases (58). A low threshold for hospital admission should exist. On discharge, patients should be placed on a controller medication (an inhaled steroid and/or leukotriene inhibitor) (58).

Despite such recommendations, significant variability exists between hospitals regarding treatment with corticosteroids (46) and other controlling medications. The debate around rebound pain has led to reluctance by some clinicians to prescribe systemic corticosteroids for patients with SCD presenting with an asthma exacerbation, whereas some evidence demonstrates the risks of asthma itself outweigh those of steroid use (58). Despite a paucity of published trials in the SCD population, in the general population, administration of systemic corticosteroids in the setting of acute asthma exacerbation has been shown to decrease admission rates and prevent symptom relapse (65, 66). It should be noted that oral, intramuscular, and intravenous administration reportedly have similar efficacy (65, 66). Additionally, inhaled corticosteroids have also been reported to decrease admission rates in the acute setting; however, it remains unclear if

they offer further benefit when combined with systemic corticosteroids (67).

PULMONARY HYPERTENSION

PH is an increasingly recognized common complication of SCD and other hereditary or acquired hemolytic anemias (2, 68). As shown in Table 1, PH has been described in case reports or series in most diseases associated with hemolytic anemia. This complication has been most studied in patients with SCD and thalassemia, who are now surviving to their fifth to seventh decades of life, likely because of improved red blood cell transfusion practice, fetal hemoglobin–inducing therapies (hydroxyurea), iron chelation therapy, and improved therapy of infectious complications (69). These patients appear to suffer from a high prevalence of pulmonary and systemic vascular disease, driven in large part by chronic anemia with a high cardiac output and high pulmonary blood flow, coupled with intravascular hemolysis, which dysregulates NO signaling, increases reactive oxygen species generation, and activates the coagulation system, in large part mediated by the pathological effects of cell-free plasma hemoglobin (10, 70).

Although early case series suggested that PH, even in the absence of thromboembolism, occurred in patients with SCD, the first comprehensive examination of this complication by Castro and colleagues (72) suggested that despite much lower mean pulmonary artery pressure (mPAP) than in patients with idiopathic pulmonary arterial hypertension (PAH) (Table 2), the associated mortality rate was very high. Each increase of 10 mm Hg in mPAP was associated with a 1.7-fold increase in the rate of death (95% CI, 1.1–2.7; $P = 0.028$) (71). A CT scan of a patient with SCD with PAH is illustrated in Figure 3.

Population Screening Studies for PH Using Doppler Echocardiography

Based on these early studies, a relatively large screening study was conducted at the NIH in Bethesda, Maryland. In the first report, 195 subjects were screened using noninvasive Doppler echocardiography, with confirmatory right heart catheterization in 18 subjects. An elevated pulmonary artery systolic pressure calculated from the TRV of greater than 2.5 m/s was prospectively defined as abnormal, based on the fact that this value is two SDs above the mean. Using the Bernoulli equation, the TRV provides a calculated estimate of right ventricular and pulmonary artery systolic pressures (PASP $\approx 4 \times$ TRV [2]) after adding an estimate of the central venous or right atrial pressure. In patients with SCD, this echocardiographic estimate has been reported to correlate well with measured pulmonary artery systolic pressures by right heart catheterization ($R = 0.77$, $P < 0.001$). This correlation is similar to that reported for Doppler echocardiography in other population groups. It should be noted that a TRV value greater than or equal to 2.5 m/s corresponds to an estimated PASP of 25 to 35 mm Hg, which is approximately two SDs above the normal mean and cannot be directly equated to a right heart catheterization definition of PH, which requires a value for a mPAP of greater than or equal to 25 mm Hg, which is three SDs above the normal mean. For patients less than 40 years of age, the mean Doppler echocardiographic estimated PASP is 27.5 ± 14.2, with a 95% CI of 19.3 to 35.5 mm Hg (72). In the NIH-PH screening study, data were analyzed for TRV stratum of less than 2.5 m/s, 2.5 to 2.9 m/s, and greater than or equal to 3 m/s, in addition to linear regression analyses, for associated risk factors and mortality.

In this study, 32% of subjects had a TRV greater than or equal to 2.5 m/s, and 9.2% greater than or equal to 3 m/s. Surprisingly, even in patients with mildly elevated TRV values, the prospective mortality was very high, with a 10-fold increase in the odds ratio (OR) for death for TRV greater than or equal to 2.5 m/s. The risk of death appears directly related to increment in estimated pulmonary systolic pressure: compared with patients with TRV less than 2.5 m/s, the rate ratio for death for a TRV of 2.5 to 2.9 m/s and greater than 3.0 m/s was 4.4 (95% CI, 1.6–12.2) and 10.6 (95% CI, 3.3–33.6), respectively (3, 11). Other noninvasive screening studies using Doppler echocardiography confirmed these results. De Castro found that 6 of 42 patients (14%) with elevated TRV and 2 of 83 patients (2%) with normal TRV died during a 2-year follow-up period (73). Similarly, a screening study by Ataga and colleagues reported that 9 of 36 patients with high TRV and 1 of 57 patients with low TRV died during the 2.5-year follow-up period (relative risk, 9.24; 95% CI, 1.2–73.3) (74).

In these studies, the development of Doppler echocardiographic–measured TRV was associated with indices of hemolytic anemia (anemia and reticulocytosis with increases in serum lactate dehydrogenase, aspartate aminotransferase, and bilirubin levels), iron overload, cholestatic liver dysfunction (elevations in alkaline phosphatase), systolic systemic hypertension, renal insufficiency, a history of cutaneous leg ulceration, and in men a history of priapism. To some surprise at the time, the number of episodes of ACS or number of vasoocclusive events did not associate with a high TRV, suggesting a more important role for hemolytic anemia and end-organ injury to kidneys and liver in the evolution of this process. This still-controversial observation is consistent with the growing appreciation that PH arises in other hemolytic diseases (Table 1) in which there is no hemoglobin S and no vasoocclusion or ACS events.

A recent large screening study using Doppler echocardiography of 483 patients with homozygous SS disease conducted in the United States and England reproduced these associations, finding that patients with elevations in Doppler-estimated pulmonary artery systolic pressures (TRV) had more severe hemolytic anemia and renal insufficiency. These patients had lower arterial oxygen saturation, higher levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) and lower walk distance in 6 minutes (75). Again, a high TRV was independent of rates of VOC or ACS, supporting the hypothesis that this complication arises secondary to chronic hemolytic anemia and end-organ dysfunction (renal and liver disease) rather than secondary to episodes of ACS and related lung fibrosis.

Population screening with Doppler echocardiography also suggests that increased PASPs occur in less hemolytic phenotypes of SCD, including Hb SC, $S\beta^+$, and S-α thalassemias, but at a lower frequency (73). One study reported a decreased incidence of high TRV among patients with SCD with hemoglobin SC (OR = 0.18;

TABLE 1. INCIDENCE OF PULMONARY HYPERTENSION AMONG DIFFERENT TYPES OF HEMOLYTIC ANEMIA

Hemolytic Anemia Type	Incidence	References
Hemoglobin SS disease	Increased	9, 73
Hemoglobin SC disease	Increased	73, 76
Hemoglobin SO_{Arab} disease	Increased	73
Hemoglobin $S\beta^+$ disease	Increased	73, 76, 98
Hemoglobin $S\beta^0$ disease	Increased	73
β-Thalassemia major	Increased	99–101
β-Thalassemia intermedia	Increased	102, 103
Hemoglobin E/β-thalassemia	Increased	104
G6PD deficiency	Not reported	
Hereditary elliptocytosis	Not reported	
Hereditary ovalocytosis	Not reported	
Hereditary spherocytosis	Increased	105
Idiopathic autoimmune	Reported	106, 107
Microangiopathic	Reported	108, 109
Paroxysmal nocturnal hemoglobinuria	Increased	110, 111
Malaria	Reported	112

TABLE 2. COMPARISON OF RIGHT HEART CATHETERIZATION REPORTS OF PULMONARY HYPERTENSION AMONG PATIENTS WITH SICKLE CELL DISEASE

	Castro *et al.*, 2003 (71)	Anthi *et al.*, 2007 (57)	Parent *et al.*, 2011 (77)	Fonseca *et al.*, 2012 (81)	Mehari *et al.*, 2012 (80)
No. subjects screened	34	43	445	80	531
Exclusion criteria	None	None	Renal insufficiency Restrictive lung disease Liver disease	None	None
Criteria for RHC	Clinical suspicion*	TRV ⩾ 2.5 m/s	TRV ⩾ 2.5 m/s	TRV ⩾ 2.5 m/s	TRV ⩾ 2.5 m/s and/or clinical suspicion
Number RHCs	39†	35	96	26	84
Number of subjects with PH‡	20	26	24	8	55
% RHC with PH	Not reported	74	25	31	65.5
% of population screened	Not reported	Not reported	6	10	10.5
Mean age of subjects with PH	37	43	45	46	41
mPAP, mm Hg	36 ± 8	37 ± 1.5	30 ± 6	33 ± 9	Not reported
PVR, dyn·s/cm^5	271 ± 90§	206 ± 23	138 ± 58	179 ± 120‖	Not reported
CO, L/min	7 ± 2§	9 ± 0.5	9 ± 2	5 ± 2¶	Not reported
6MWD, m	Not reported	320 ± 20	404 ± 94	460 ± 152	358 ± 113
Duration of follow-up, yr	1.9**	Not reported	2.2	2.8††	4.4**
Mortality in PH group	55%	Not reported	23%	38%	37%

Definition of abbreviations: 6MWD = 6-min walk distance; CO = cardiac output; mPAP = mean pulmonary artery pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RHC = right heart catheterization.

* Clinical suspicion reported as: increased intensity of second heart sound in pulmonic area, right side cardiac chamber enlargement by chest X-ray or electrocardiogram, or abnormal echocardiography.

† Five of 34 patients had one or more follow-up procedures.

‡ Pulmonary hypertension defined as mPAP ⩾ 25 mm Hg.

§ Data only reported for subgroup of eight patients.

‖ Converted mean value: PVR measured in Wood units as 2.24 ± 1.5.

¶ Cardiac index (L/min/m^2).

** Median.

†† Estimated from figure in Reference 81.

95% CI, 0.06–0.51; $P = 0.0005$) or Sβ^+ thalassemia (OR = 0.25; 95% CI, 0.06–1.16; $P = 0.10$) phenotypes (76). Although these compound heterozygotes may be protected from PH because of reduced levels of intravascular hemolysis, they may still develop this complication at a lower prevalence due to the presence of nonhemolytic risk factors such as renal dysfunction, iron overload, and advancing age (76).

Operating Characteristics of Doppler Echocardiographic Screening for PH in Patients with SCD

As mentioned earlier, the Doppler echocardiogram is an important tool for population-based estimates of PASP elevation, but it cannot be used to define PAH, which is a right heart catheter–based diagnosis defined by the elevation of the mPAP greater than or equal to 25 mm Hg and a pulmonary artery occlusion pressure of less than 15 mm Hg. Note that PASPs can rise with both right (PAH) and left (pulmonary venous hypertension [PVH]) heart failure, and to a lesser degree with very high cardiac outputs. Parent and colleagues performed a screening study of PH in 398 patients with SCD in France, using Doppler echocardiography and confirmation by right heart catheterization, described in more detail later (77). They found that only 25% of patients with a Doppler echocardiographic screening TRV greater than or equal to 2.5 m/s had PH diagnosed by right heart catheterization. If they used a TRV greater than

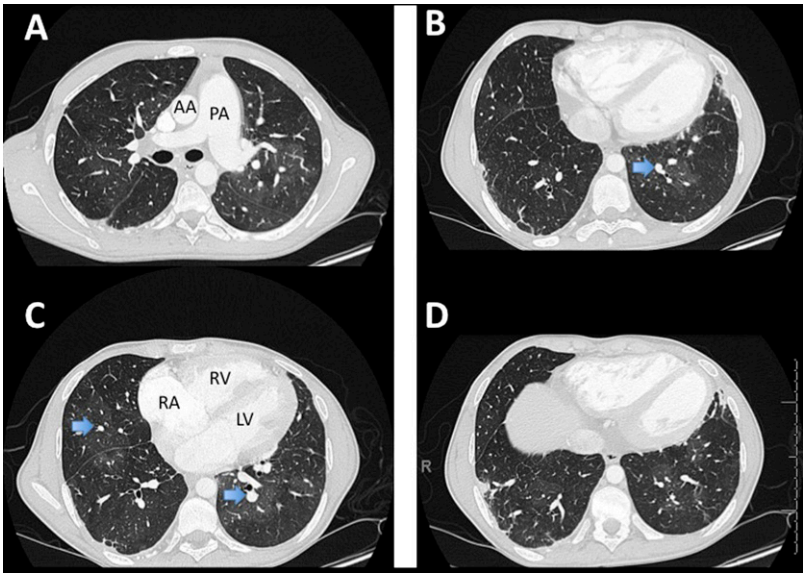

Figure 3. Radiographic findings of pulmonary hypertension in an 18-year-old patient with sickle cell disease. (*A*) Note the central pulmonary artery (PA) is enlarged and significantly larger than the adjacent ascending aorta (AA), indicating a PA/AA ratio greater than 1. (*B*, *C*) Relative increase in segmental artery size relative to adjacent bronchus (*arrows*) as well as loss of peripheral vascularity. (*C*) Note right ventricle (RV) is hypertrophied and dilated with evidence of right atrial (RA) dilation. All images illustrate the finding of mosaic perfusion pattern of parenchymal attenuation.

or equal to 2.9 m/s, the positive predictive value increased from 25 to 64%, but the false-negative rate was 42%, unacceptable considering the high risk related to PH. By using a TRV greater than or equal to 2.5 m/s and a high NT-proBNP (>164.5 pg/ml) and a low walk distance of less than 333 m, the positive predictive value was 62%, with a false-negative rate of 7%. Based on these data, a modified screening algorithm is proposed for adult patients with SCD (Figure 4).

Evaluation of PH Hemodynamics, Prevalence, Risk Factors, and Associated Mortality Using Definitive Measures by Right Heart Catheterization

Most patients with PH associated with SCD have mild disease when judged by cardiopulmonary hemodynamics, yet the associated mortality is unexpectedly high (57, 74, 78, 79). Although classified as a subgroup of Group I PAH, similar to scleroderma, patients with SCD often present with PVH secondary to left ventricular diastolic dysfunction (approximately 40% of PH cases have PVH). Right heart catheterization studies of patients with SCD and PH reveal a hyperdynamic state similar to the hemodynamics characteristic of portopulmonary hypertension (57, 71). The mPAP in patients with SCD and PAH is approximately 36.6 ± 1.5 mm Hg and pulmonary vascular resistance approximately 206.1 ± 22.8 dyn·s/cm^5 (57). The relatively low pulmonary vascular resistance is caused by the high cardiac output and low viscosity of anemia, both of which lower the pulmonary vascular resistance. Approximately one-half of catheterized patients with PH (mean PAP ⩾ 25 mm Hg) meet the definition of PAH, indicating that vasculopathy primarily involves the pulmonary arterial system but can also develop as a consequence of left-sided disease. In the other half of subjects, the left ventricular end-diastolic pressures are greater than 15 mm Hg, indicating a component of left ventricular diastolic dysfunction (57). Patients with both pulmonary vascular disease and echocardiographic evidence of diastolic dysfunction are at a particularly high risk of death (relative risk ratio, 12.0; 95% CI, 3.8–38.1; $P < 0.001$) (75).

Three new studies now provide additional insights based on definitive right heart catheterization (Table 2). The NIH screening study, first published with 195 patients in 2004, has now been extended for 9 years of follow-up in 533 patients (2001–2010, median follow-up of 4.4 yr) (80). A total of 86 subjects underwent right heart catheterization over this time period, and of these, 56 patients were diagnosed with PH defined by mean PAP greater than or equal to 25 mm Hg (10.5% of the 533 patients evaluated). This 10.5% prevalence estimate of PH defined by right heart catheterization may represent a conservative number, as only half of the patients with TRV greater than 2.5 underwent right heart catheterization in this cohort. Consistent with prior studies, approximately half of these patients had PAH and half PVH (57). During a median follow-up of 4.4 years, mortality rate was significantly higher in the PH group overall (20 deaths, 36%) than either the group without PH by right heart catheterization (3 deaths, 10%, $P = 0.043$) or the general sickle cell group with normal Doppler echocardiographic estimates of PH (50 deaths, 13%, $P < 0.0001$).

These observations have also been observed in a second screening study of patients with SCD in Brazil, which revealed a 10% prevalence of PH defined by right heart catheterization in patients with SCD screened in Brazil (81). Similar to the NIH screening study, not all patients with a high TRV value underwent right heart catheterization. This study also confirmed associations with hemolytic anemia, renal insufficiency, exercise intolerance, and high associated mortality risk (38% in PH group) (81).

A third large Doppler echocardiogram and hemodynamic screening study of PH in 398 patients with SCD in France has now been published (77). Parent and colleagues observed a similar prevalence of echocardiographic estimates of elevated pulmonary artery systolic pressure (31% prevalence of TRV ⩾ 2.5 m/s in the U.S. cohort and 27% in the French cohort), as well as similar values for TRV greater than 2.9 m/s (78). Using a right heart catheterization definition of PH of mPAP greater than or equal to 25 mm Hg, a value that defines PH but is three SDs above the normal mean, they found that 6% had PH.

The French study confirmed risk factors associated with PH, which had been previously identified by Doppler echocardiography (11), using gold standard right heart catheter–based definition, including renal insufficiency, markers of hemolysis

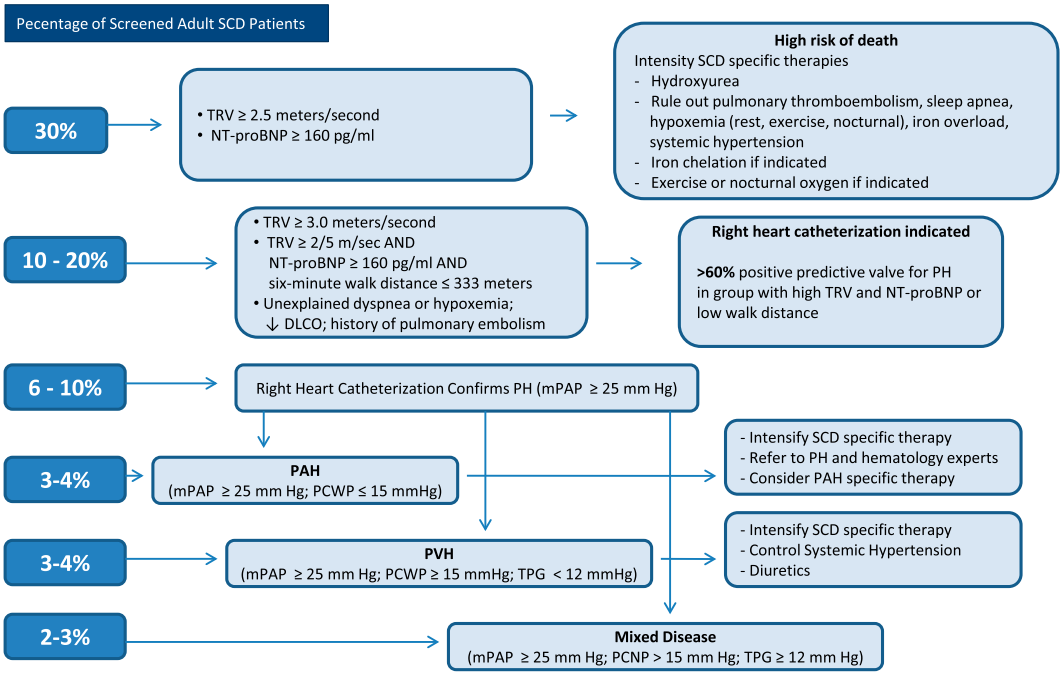

Figure 4. Screening and treatment approach for adult patients with sickle cell disease (SCD). The role of screening Doppler echocardiography, plasma N-terminal pro-brain natriuretic peptide (NT-proBNP), and 6-minute walk, with confirmation by right heart catheterization, is outlined. The prevalence and hemodynamic definitions of cardiopulmonary abnormalities found on screening are summarized. mPAP = mean pulmonary artery pressure; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; TRV = tricuspid regurgitant jet velocity.

(lactate dehydrogenase and aspartate aminotransferase released by red cells, but not alanine aminotransferase, which is specific for hepatocytes) and markers of liver dysfunction (increased alkaline phosphatase and direct bilirubin). From a clinical standpoint, the study confirmed the relationships between PH and cutaneous leg ulceration, low exercise capacity, and increased risk of death (12.5% in PH group vs. 0.3% in non-PH group; $P = 0.002$), and lack of association with VOC and ACS (3, 11).

In terms of differences in PH prevalence estimates between the French study and both the U.S. and Brazilian studies, a major difference in study design is that Parent and colleagues (78) excluded approximately 10% of patients, those with "severe" renal, liver, or lung disease. It is not clear why these are referred to as severe complications. Severity was defined as a creatinine clearance of less than 30 ml/min, an abnormal prothrombin time (international normalized ratio > 1.7), and chronic restrictive lung disease defined by a TLC of less than 70% predicted. For reference, the threshold of TLC used is classified by the ATS as a moderate reduction. It is also not clear why these patients would be excluded from a prevalence study of SCD-related PAH, especially considering the fact that all of these complications develop as a direct consequence of SCD and all three represent significant published risk factors for developing PH in SCD (11, 57, 82). For example, in our recent Walk-PHASST screening study, 24 of 375 (6.4%) adult patients with HbSS had a creatinine clearance less than 30 ml/min estimated by the Cockcroft-Gault formula (75). Of these, 22 (91.7%) had a TRV greater than or equal to 2.5 m/s and 13 (54.2%) had a TRV greater than or equal to 3.0 m/s, indicating the likely high prevalence of PH in these excluded patients. It is notable that if half of the patients excluded had PH, the prevalence of PH in the Parent and colleagues study (77) would be similar to that observed in the U.S. and Brazilian screening studies. The exclusion of these subjects not only has the potential to affect prevalence estimates but also can affect calculations of the operating characteristics of screening tests. For example, the positive predictive value of Doppler echocardiography is reduced by a lower measured population prevalence.

Caveat: An Increased Risk of Borderline PH in Patients with SCD?

A major outstanding question is the risk of borderline elevations in mPAP in patients with SCD. Note that the current PH definition of resting mPAP greater than or equal to 25 mm Hg is approximately three SDs above normal and was established based on populations with idiopathic PAH, typically presenting with single-organ dysfunction (83). It is possible that borderline increases in mPAP, between 20 and 25 mm Hg, could influence clinical outcomes in patients with SCD or other systemic diseases. This can be considered analogous to the patient with PAH who becomes pregnant or develops sepsis. More severe anemia and high cardiac output increase the risk of right heart failure at any given severity of pulmonary vascular disease. It has been shown that patients with scleroderma have measurable changes in exercise function at mPAP lower than 25 mm Hg. In these patients, even a mildly elevated resting mPAP (even >17 mm Hg) is associated with lower maximal work rate, $\dot{V}O_2$, and 6-minute walk distance (6MWD), despite a mean pulmonary vascular resistance of only 168 ± 47 dyn·s/cm^5 (84). Future studies evaluating patients with borderline elevations in mPAP with longer follow-up times will be required to address this important question.

Pulmonary Embolism and Chronic Thromboembolic Pulmonary Hypertension

Chronic thromboembolic PH can occur in patients with SCD. Approximately 5% of patients identified with PH by right heart catheterization at the NIH had a high probability $\dot{V}/\dot{Q}$ scan or history of pulmonary embolism; however, a frank diagnosis of chronic thromboembolic PH is rare (57, 85). This diagnosis should be considered and evaluated in all patients with SCD and significant PH, particularly in younger patients or those without other typical risk factors (severe hemolytic anemia or renal failure, for example). Successful thromboembolectomy in patients with SCD has been described (86).

Management and Specific Therapy for SCD-associated Pulmonary Hypertension

Owing to the lack of large clinical trial data for specific therapy of PH in patients with SCD, current recommendations focus on primary control of the hematological disease with hydroxyurea therapy, transfusions, and control of other associated factors, such as iron overload, hypoxemia, and other end-organ complications. There have been no prospective trials of hydroxyurea or transfusions for patients with SCD and PH; these recommendations are based on the known efficacy of hydroxyurea and transfusions in reducing VOC and ACS event rates (44), which would be expected to increase the risk of death in a patient with significant PH (19). In patients with SCD with PAH hemodynamics (Group I) confirmed by right heart catheterization (mean PAP $\geqslant$ 25 mm Hg and pulmonary artery occlusion pressures < 15 mm Hg, with a relatively high pulmonary vascular resistance > 160 dyn·s/cm^5), PAH-specific therapy can be considered. Therapy should be initiated and monitored by a team composed of a PAH specialist and a hematologist specializing in SCD care.

Phosphodiesterase 5 inhibitors. NO exerts its vascular effects principally by binding and activating soluble guanylyl cyclase, boosting intracellular cyclic guanosine monophosphate (cGMP) levels (87, 88). In pulmonary vasculature, this is counterbalanced by the phosphodiesterase-5 (PDE-5) enzyme, which hydrolyzes cGMP. PDE-5 inhibitors delay cGMP breakdown, thereby prolonging and amplifying NO-mediated signals (87). Additionally, PDE-5 inhibitors have been shown to restore platelet activation to more normal levels in patients with SCD-PH (89).

Of note, the PDE-5 inhibitor sildenafil is approved by the Food and Drug Administration to treat PAH in the general population. Early data suggest sildenafil may improve SCD-PH (88). In a pilot study, sildenafil therapy used in patients with SCD for approximately 6 months decreased the mean estimated PASP from 50 (4) mm Hg to 41 (3) mm Hg (difference, 9 mm Hg; 95% CI, 0.3–17 mm Hg; $P = 0.04$) and improved the mean 6MWD from 384 m (30) to 462 m (28) (difference, 78 m; 95% CI, 40–117; $P = 0.001$) (88). Confirmatory data have been reported in SCD and thalassemia (90). However, these data were not supported by a recent NIH-sponsored multicenter clinical trial of sildenafil in SCD-PH (82). This 16-week, double-blind placebo-controlled trial of 74 patients with SCD-PH assessing exercise capacity in patients with increased TRV and a low exercise capacity was stopped early, before enrollment of the planned 132 patients, due to a higher percentage of subjects experiencing serious adverse events in the sildenafil arm (45% of sildenafil, 22% placebo, $P = 0.022$). Subject hospitalization for pain was the predominant cause for this difference: 35% sildenafil versus 14% placebo ($P = 0.029$) (82). Based on known effects of PDE-5 inhibitors causing back pain and myalgias, it has been hypothesized that this medication lowered pain thresholds in patients with SCD (82). Although underpowered at the time the study

was stopped, there was no evidence of a treatment effect on 6MWD (placebo-corrected effect, −9 m; 95% CI, −56 to 38; $P = 0.703$), TRV ($P = 0.503$), or NT-proBNP ($P = 0.410$) (82).

Based on these data, the PDE5 inhibitors should not be used as first-line agents in patients with SCD and PAH. If used, it should only be in patients on chronic transfusion therapy or very well controlled with hydroxyurea, to limit the apparent effects of the PDE-5 inhibitors on increasing pain in patients with SCD. Further investigation regarding the safety and therapeutic efficacy of these treatment regimens for SCD-PH is warranted.

Endothelin receptor blockade. Endothelin (ET) is a potent endogenous vasoconstrictor that plays an important role in the pathogenesis of PAH. Its three isoforms (ET-1, -2, and -3) are produced primarily by vascular endothelial cells (91). ET-1 mediates its effects through two receptor subtypes, ET_A and ET_B. NO normally represses ET-1 secretion and high levels are commonly found in low NO states (87). ET-1 is present at pathologically high levels in PAH and ET receptor antagonists (ERA) are approved for PAH treatment (bosentan and ambrisentan) (87).

In an open-label, nonblinded cohort of 17 patients with SCD-PAH undergoing ERA treatment with either bosentan or ambrisentan, ERA treatment resulted in lower NT-proBNP levels and TRV measurements, suggesting improvement in fluid retention and PH. Among the three patients with post-therapy repeat right heart catheterization, there was a trend toward lower mPAP. Additionally, the 6MWD increased significantly over 6 months, suggesting improved cardiopulmonary functional performance (92). There was also a trend toward improved Borg Dyspnea Score and New York Heart Association classification (92). Adverse events while on therapy occurred in 7 of 14 patients, including: increased serum alanine aminotransferase (two), increased peripheral edema (four), rash (one), headache (three), and decreased hemoglobin (two). Only two patients required treatment discontinuation, and few patients experienced multiple side effects (92).

The ASSET-1 and -2 trials set out to assess the effects of ERA therapy with Bosentan on patients with PAH and PVH, respectively. Although well tolerated and apparently safe, the studies were terminated due to slow site initiation and patient enrolment (n = 26), and efficacy end point analysis was limited by low power (93).

Unfortunately, the clinical data assessing the usefulness of ERA therapy for SCD-PH is still insufficient. There remain concerns about using agents approved for PAH to treat patients with SCD-PH without larger safety and efficacy studies. Prostanoid use is associated with the risk of line sepsis or thrombosis and may potentially exacerbate a hyperdynamic state. ERAs are associated with a risk of hepatotoxicity, which is important in patients with SCD as they are predisposed to develop cirrhosis secondary to hepatitis C and iron overload from repeated transfusions (94). Decrease in hemoglobin may also be of concern for bosentan.

Taken together, our approach is to maximize SCD-specific therapy in patients with PAH using hydroxyurea, iron chelation, blood transfusions, and oxygen as indicated, and in patients with Group I hemodynamic PAH defined by right heart catheterization, we will start with an ERA (ambrisentan has less risk of hepatotoxicity) coupled to diuresis to control right heart failure. PDE-5 inhibitors and prostanoids are reserved for patients with more severe disease, with evidence of right heart failure well managed on a chronic simple or exchange transfusion program to maintain HbS levels less than 20%.

Other therapies. A multitude of other therapies have been tested for efficacy in the SCD-PH population, including inhaled NO and arginine supplementation. In general, these endeavors have met with modest or insignificant results.

Based on the premise that an increase in endogenous NO synthase inhibitors may result in a relative NO deficiency in the pulmonary vasculature, NO supplementation was investigated for therapeutic efficacy. It was hypothesized that inhaled NO gas would preferentially react with the circulating plasma hemoglobin in the pulmonary vasculature to oxidize it to methemoglobin, thereby preventing NO scavenging and limiting the systemic vasopressor effects of plasma hemoglobin. Despite conflicting evidence for the use of inhaled NO for the treatment of VOC (18, 53), evidence for its usefulness in the prevention or management of SCD-associated PH is lacking.

Arginine supplementation has also been studied. Ordinarily, L-arginine is converted by NO synthase to citrulline plus NO (95). Arginine dysregulation has been associated with reduced NO bioavailability and some SCD complications. In SCD, it is believed that increased arginase activity results in a relative deficiency and decreased NO production. Oral arginine supplementation has been reported to increase exhaled NO levels in both patients with SCD and healthy control subjects (96). Administration of large arginine doses appeared to reduce pulmonary pressures in patients with SCD-PH. A study of 10 patients with SCD reported that oral arginine (0.1 g/kg) produced a 15.2% mean reduction in estimated PASP from 63.9 (13) mm Hg to 54.2 (12) mm Hg ($P = 0.002$) after 5 days of therapy (97). In another study of adults on hydroxyurea, addition of high-dose arginine for 3 months doubled the plasma arginine levels (47 ± 16 to 96 ± 58 μM, n = 8, $P < 0.005$) but did not change the TRV (2.57 ± 0.32 to 2.72 ± 0.40 m/s, n = 9, P = not significant) (95). It is not clear whether in this trial hydroxyurea may have obscured beneficial effects of arginine supplementation on TRV or hematologic parameters. The true efficacy and potential adverse effects of long-term very high dose arginine have not been examined adequately, and right heart catheterization end points have not been evaluated. Although it is available as a dietary supplement without a prescription, providers and patients should be cautious about adopting it until more research is completed (95).

In patients with evident diastolic dysfunction and elevated left ventricular diastolic pressures and/or central venous pressures, diuresis and systemic blood pressure control should be considered. In our experience, diuresis for evident right heart failure is well tolerated and can improve patient symptoms.

CONCLUSIONS

SCD is a common monogenetic disorder with high associated morbidity and mortality. The complications of SCD are myriad; however, pulmonary complications are common. In addition to ACD and asthma, concomitant PH significantly increases morbidity and/or mortality. Doppler echocardiographic screening of adults with SCD can identify a high-risk population that may benefit from intensification of sickle cell–specific therapy, such as hydroxyurea or exchange transfusions. The diagnosis of PH should be confirmed by definitive right heart catheterization, and referral for management by skilled specialists in SCD and PH is recommended. Patients with PH may have treatable comorbidities, such as iron overload, sleep-disordered breathing, nocturnal or exercise desaturation, pulmonary thromboembolic diseases, severe hemolytic anemia, or frequent VOC and ACS. For patients diagnosed with PAH by right heart catheterization, referral for clinical trials is recommended; PH-specific therapy can be considered judiciously in the absence of definitive clinical trials outcome data.

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1. Kato GJ, Gladwin MT, Steinberg MH. Deconstructing sickle cell disease: reappraisal of the role of hemolysis in the development of clinical subphenotypes. *Blood Rev* 2007;21:37–47.

2. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. *Lancet* 2010; 376:2018–2031.
3. Gladwin MT, Vichinsky E. Pulmonary complications of sickle cell disease. *N Engl J Med* 2008;359:2254–2265.
4. Aliyu ZY, Gordeuk V, Sachdev V, Babadoko A, Mamman AI, Akpanpe P, Attah E, Suleiman Y, Aliyu N, Yusuf J, *et al.* Prevalence and risk factors for pulmonary artery systolic hypertension among sickle cell disease patients in Nigeria. *Am J Hematol* 2008;83:485–490.
5. Platt OS. The acute chest syndrome of sickle cell disease. *N Engl J Med* 2000;342:1904–1907.
6. Brittenham GM, Schechter AN, Noguchi CT. Hemoglobin S polymerization: primary determinant of the hemolytic and clinical severity of the sickling syndromes. *Blood* 1985;65:183–189.
7. Bunn HF. Pathogenesis and treatment of sickle cell disease. *N Engl J Med* 1997;337:762–769.
8. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, Klug PP. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med* 1994;330:1639–1644.
9. Vichinsky EP, Neumayr LD, Earles AN, Williams R, Lennette ET, Dean D, Nickerson B, Orringer E, McKie V, Bellevue R, *et al.* Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. *N Engl J Med* 2000;342:1855–1865.
10. Reiter CD, Wang X, Tanus-Santos JE, Hogg N, Cannon RO 3rd, Schechter AN, Gladwin MT. Cell-free hemoglobin limits nitric oxide bioavailability in sickle-cell disease. *Nat Med* 2002;8:1383–1389.
11. Gladwin MT, Sachdev V, Jison ML, Shizukuda Y, Plehn JF, Minter K, Brown B, Coles WA, Nichols JS, Ernst I, *et al.* Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. *N Engl J Med* 2004;350:886–895.
12. Perronne V, Roberts-Harewood M, Bachir D, Roudot-Thoraval F, Delord JM, Thuret I, Schaeffer A, Davies SC, Galacteros F, Godeau B. Patterns of mortality in sickle cell disease in adults in France and England. *Hematol J* 2002;3:56–60.
13. Fartoukh M, Lefort Y, Habibi A, Bachir D, Galacteros F, Godeau B, Maitre B, Brochard L. Early intermittent noninvasive ventilation for acute chest syndrome in adults with sickle cell disease: a pilot study. *Intensive Care Med* 2010;36:1355–1362.
14. Boyd JH, Moinuddin A, Strunk RC, DeBaun MR. Asthma and acute chest in sickle-cell disease. *Pediatr Pulmonol* 2004;38:229–232.
15. Sylvester KP, Patey RA, Broughton S, Rafferty GF, Rees D, Thein SL, Greenough A. Temporal relationship of asthma to acute chest syndrome in sickle cell disease. *Pediatr Pulmonol* 2007;42:103–106.
16. Vichinsky EP, Styles LA, Colangelo LH, Wright EC, Castro O, Nickerson B. Acute chest syndrome in sickle cell disease: clinical presentation and course. Cooperative Study of Sickle Cell Disease. *Blood* 1997;89:1787–1792.
17. Reagan MM, DeBaun MR, Frei-Jones MJ. Multi-modal intervention for the inpatient management of sickle cell pain significantly decreases the rate of acute chest syndrome. *Pediatr Blood Cancer* 2011;56:262–266.
18. Gladwin MT, Kato GJ, Weiner D, Onyekwere OC, Dampier C, Hsu L, Hagar RW, Howard T, Nuss R, Okam MM, *et al.* Nitric oxide for inhalation in the acute treatment of sickle cell pain crisis: a randomized controlled trial. *JAMA* 2011;305:893–902.
19. Mekontso Dessap A, Leon R, Habibi A, Nzouakou R, Roudot-Thoraval F, Adnot S, Godeau B, Galacteros F, Brun-Buisson C, Brochard L, *et al.* Pulmonary hypertension and cor pulmonale during severe acute chest syndrome in sickle cell disease. *Am J Respir Crit Care Med* 2008;177:646–653.
20. Boyd JH, Macklin EA, Strunk RC, DeBaun MR. Asthma is associated with acute chest syndrome and pain in children with sickle cell anemia. *Blood* 2006;108:2923–2927.
21. Cohen RT, DeBaun MR, Blinder MA, Strunk RC, Field JJ. Smoking is associated with an increased risk of acute chest syndrome and pain among adults with sickle cell disease. *Blood* 2010;115:3852–3854.
22. Poulter EY, Truszkowski P, Thompson AA, Liem RI. Acute chest syndrome is associated with history of asthma in hemoglobin SC disease. *Pediatr Blood Cancer* 2011;57:289–293.
23. Bernaudin F, Strunk RC, Kamdem A, Arnaud C, An P, Torres M, Delacourt C, DeBaun MR. Asthma is associated with acute chest syndrome, but not with an increased rate of hospitalization for pain among children in France with sickle cell anemia: a retrospective cohort study. *Haematologica* 2008;93:1917–1918.
24. Knight-Madden JM, Forrester TS, Lewis NA, Greenough A. Asthma in children with sickle cell disease and its association with acute chest syndrome. *Thorax* 2005;60:206–210.
25. Sen N, Kozanoglu I, Karatasli M, Ermis H, Boga C, Eyuboglu FO. Pulmonary function and airway hyperresponsiveness in adults with sickle cell disease. *Lung* 2009;187:195–200.
26. Strouse JJ, Reller ME, Bundy DG, Amoako M, Cancio M, Han RN, Valsamakis A, Casella JF. Severe pandemic H1N1 and seasonal influenza in children and young adults with sickle cell disease. *Blood* 2010;116:3431–3434.
27. Miller AC, Safi F, Hussain S, Subramanian RA, Elamin EM, Sinert R. Novel influenza A(H1N1) virus among gravid admissions. *Arch Intern Med* 2010;170:868–873.
28. Miller AC, Subramanian RA, Safi F, Sinert R, Zehtabchi S, Elamin EM. Influenza A 2009 (H1N1) virus in admitted and critically ill patients. *J Intensive Care Med* 2012;27:25–31.
29. Holtzclaw JD, Jack D, Aguayo SM, Eckman JR, Roman J, Hsu LL. Enhanced pulmonary and systemic response to endotoxin in transgenic sickle mice. *Am J Respir Crit Care Med* 2004;169:687–695.
30. Sabaa N, de Franceschi L, Bonnin P, Castier Y, Malpeli G, Debbabi H, Galaup A, Maier-Redelsperger M, Vandermeersch S, Scarpa A, *et al.* Endothelin receptor antagonism prevents hypoxia-induced mortality and morbidity in a mouse model of sickle-cell disease. *J Clin Invest* 2008;118:1924–1933.
31. Gladwin MT, Rodgers GP. Pathogenesis and treatment of acute chest syndrome of sickle-cell anaemia. *Lancet* 2000;355:1476–1478.
32. Styles LA, Schalkwijk CG, Aarsman AJ, Vichinsky EP, Lubin BH, Kuypers FA. Phospholipase A2 levels in acute chest syndrome of sickle cell disease. *Blood* 1996;87:2573–2578.
33. Lechapt E, Habibi A, Bachir D, Galacteros F, Schaeffer A, Desvaux D, Brochard L, Housset B, Godeau B, Maitre B. Induced sputum versus bronchoalveolar lavage during acute chest syndrome in sickle cell disease. *Am J Respir Crit Care Med* 2003;168:1373–1377.
34. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 34–1997. A 22-year-old man with a sickle cell crisis and sudden death. *N Engl J Med* 1997;337:1293–1301.
35. Pruchnicki A. First, do no harm (pending prior approval). *N Engl J Med* 1997;337:1627–1628.
36. Mekontso Dessap A, Deux JF, Abidi N, Lavenu-Bombled C, Melica G, Renaud B, Godeau B, Adnot S, Brochard L, Brun-Buisson C, *et al.* Pulmonary artery thrombosis during acute chest syndrome in sickle cell disease. *Am J Respir Crit Care Med* 2011;184:1022–1029.
37. Chen J, Hobbs WE, Le J, Lenting PJ, de Groot PG, Lopez JA. The rate of hemolysis in sickle cell disease correlates with the quantity of active von Willebrand factor in the plasma. *Blood* 2011;117:3680–3683.
38. Zhou Z, Han H, Cruz MA, Lopez JA, Dong JF, Guchhait P. Haemoglobin blocks von Willebrand factor proteolysis by ADAMTS-13: a mechanism associated with sickle cell disease. *Thromb Haemost* 2009;101:1070–1077.
39. Zhou Z, Behymer M, Guchhait P. Role of extracellular hemoglobin in thrombosis and vascular occlusion in patients with sickle cell anemia. *Anemia* 2011;2011:918916.
40. Styles LA, Aarsman AJ, Vichinsky EP, Kuypers FA. Secretory phospholipase A(2) predicts impending acute chest syndrome in sickle cell disease. *Blood* 2000;96:3276–3278.
41. Styles LA, Abboud M, Larkin S, Lo M, Kuypers FA. Transfusion prevents acute chest syndrome predicted by elevated secretory phospholipase A2. *Br J Haematol* 2007;136:343–344.
42. Vichinsky EP, Haberkern CM, Neumayr L, Earles AN, Black D, Koshy M, Pegelow C, Abboud M, Ohene-Frempong K, Iyer RV. A comparison of conservative and aggressive transfusion regimens in the perioperative management of sickle cell disease. The Preoperative Transfusion in Sickle Cell Disease Study Group. *N Engl J Med* 1995;333:206–213.
43. Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma Management Program Research Group. *N Engl J Med* 2000;343:1054–1063.
44. Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, McMahon RP, Bonds DR. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter

Study of Hydroxyurea in Sickle Cell Anemia. *N Engl J Med* 1995;332: 1317–1322.
45. Bellet PS, Kalinyak KA, Shukla R, Gelfand MJ, Rucknagel DL. Incentive spirometry to prevent acute pulmonary complications in sickle cell diseases. *N Engl J Med* 1995;333:699–703.
46. Sobota A, Graham DA, Heeney MM, Neufeld EJ. Corticosteroids for acute chest syndrome in children with sickle cell disease: variation in use and association with length of stay and readmission. *Am J Hematol* 2010;85:24–28.
47. Emre U, Miller ST, Gutierez M, Steiner P, Rao SP, Rao M. Effect of transfusion in acute chest syndrome of sickle cell disease. *J Pediatr* 1995;127:901–904.
48. Alhashimi D, Fedorowicz Z, Alhashimi F, Dastgiri S. Blood transfusions for treating acute chest syndrome in people with sickle cell disease. *Cochrane Database Syst Rev* 2010;2010:CD007843.
49. Vij R, Machado RF. Pulmonary complications of hemoglobinopathies. *Chest* 2010;138:973–983.
50. Darbari DS, Castro O, Taylor JG 6th, Fasano R, Rehm J, Gordeuk VR, Minniti CP. Severe vaso-occlusive episodes associated with use of systemic corticosteroids in patients with sickle cell disease. *J Natl Med Assoc* 2008;100:948–951.
51. Strouse JJ, Hulbert ML, DeBaun MR, Jordan LC, Casella JF. Primary hemorrhagic stroke in children with sickle cell disease is associated with recent transfusion and use of corticosteroids. *Pediatrics* 2006; 118:1916–1924.
52. Strouse JJ, Takemoto CM, Keefer JR, Kato GJ, Casella JF. Corticosteroids and increased risk of readmission after acute chest syndrome in children with sickle cell disease. *Pediatr Blood Cancer* 2008;50:1006–1012.
53. Weiner DL, Hibberd PL, Betit P, Cooper AB, Botelho CA, Brugnara C. Preliminary assessment of inhaled nitric oxide for acute vaso-occlusive crisis in pediatric patients with sickle cell disease. *JAMA* 2003;289:1136–1142.
54. Head CA, Swerdlow P, McDade WA, Joshi RM, Ikuta T, Cooper ML, Eckman JR. Beneficial effects of nitric oxide breathing in adult patients with sickle cell crisis. *Am J Hematol* 2010;85:800–802.
55. Powars D, Weidman JA, Odom-Maryon T, Niland JC, Johnson C. Sickle cell chronic lung disease: prior morbidity and the risk of pulmonary failure. *Medicine (Baltimore)* 1988;67:66–76.
56. Klings ES, Wyszynski DF, Nolan VG, Steinberg MH. Abnormal pulmonary function in adults with sickle cell anemia. *Am J Respir Crit Care Med* 2006;173:1264–1269.
57. Anthi A, Machado RF, Jison ML, Taveira-Dasilva AM, Rubin LJ, Hunter L, Hunter CJ, Coles W, Nichols J, Avila NA, *et al.* Hemodynamic and functional assessment of patients with sickle cell disease and pulmonary hypertension. *Am J Respir Crit Care Med* 2007;175:1272–1279.
58. Morris CR. Asthma management: reinventing the wheel in sickle cell disease. *Am J Hematol* 2009;84:234–241.
59. Boyd JH, Macklin EA, Strunk RC, DeBaun MR. Asthma is associated with increased mortality in individuals with sickle cell anemia. *Haematologica* 2007;92:1115–1118.
60. Field JJ, DeBaun MR. Asthma and sickle cell disease: two distinct diseases or part of the same process? *Hematology Am Soc Hematol Educ Program* 2009:45–53.
61. Bryant R. Asthma in the pediatric sickle cell patient with acute chest syndrome. *J Pediatr Health Care* 2005;19:157–162.
62. Nordness ME, Lynn J, Zacharisen MC, Scott PJ, Kelly KJ. Asthma is a risk factor for acute chest syndrome and cerebral vascular accidents in children with sickle cell disease. *Clin Mol Allergy* 2005;3:2.
63. Cohen RT, Madadi A, Blinder MA, DeBaun MR, Strunk RC, Field JJ. Recurrent, severe wheezing is associated with morbidity and mortality in adults with sickle cell disease. *Am J Hematol* 2011;86:756–761.
64. National Heart, Lung, and Blood Institute (NHLBI). Expert Panel Report$_3$ (EPR$_3$): guidelines for the diagnosis and management of asthma [Internet; accessed 2011 Aug 1]. Available from: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm
65. Rowe BH, Keller JL, Oxman AD. Effectiveness of steroid therapy in acute exacerbations of asthma: a meta-analysis. *Am J Emerg Med* 1992;10:301–310.
66. Rowe BH, Spooner CH, Ducharme FM, Bretzlaff JA, Bota GW. Corticosteroids for preventing relapse following acute exacerbations of asthma. *Cochrane Database Syst Rev* 2007;2007:CD000195.
67. Edmonds ML, Camargo CA Jr, Pollack CV Jr, Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. *Cochrane Database Syst Rev* 2003;2003:CD002308.
68. Jison ML, Gladwin MT. Hemolytic anemia-associated pulmonary hypertension of sickle cell disease and the nitric oxide/arginine pathway. *Am J Respir Crit Care Med* 2003;168:3–4.
69. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. *Lancet.* 2010; 376:2018–2031.
70. Rother RP, Bell L, Hillmen P, Gladwin MT. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease. *JAMA* 2005;293:1653–1662.
71. Castro O, Hoque M, Brown BD. Pulmonary hypertension in sickle cell disease: cardiac catheterization results and survival. *Blood* 2003;101: 1257–1261.
72. McQuillan BM, Picard MH, Leavitt M, Weyman AE. Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. *Circulation* 2001;104:2797–2802.
73. De Castro LM, Jonassaint JC, Graham FL, Ashley-Koch A, Telen MJ. Pulmonary hypertension associated with sickle cell disease: clinical and laboratory endpoints and disease outcomes. *Am J Hematol* 2008;83:19–25.
74. Ataga KI, Moore CG, Jones S, Olajide O, Strayhorn D, Hinderliter A, Orringer EP. Pulmonary hypertension in patients with sickle cell disease: a longitudinal study. *Br J Haematol* 2006;134:109–115.
75. Sachdev V, Kato GJ, Gibbs JS, Barst RJ, Machado RF, Nouraie M, Hassell KL, Little JA, Schraufnagel DE, Krishnamurti L, *et al.* Echocardiographic markers of elevated pulmonary pressure and left ventricular diastolic dysfunction are associated with exercise intolerance in adults and adolescents with homozygous sickle cell anemia in the United States and United Kingdom. *Circulation* 2011;124:1452–1460.
76. Taylor JG 6th Ackah D, Cobb C, Orr N, Percy MJ, Sachdev V, Machado R, Castro O, Kato GJ, Chanock SJ, *et al.* Mutations and polymorphisms in hemoglobin genes and the risk of pulmonary hypertension and death in sickle cell disease. *Am J Hematol* 2008;83:6–14.
77. Parent F, Bachir D, Inamo J, Lionnet F, Driss F, Loko G, Habibi A, Bennani S, Savale L, Adnot S, *et al.* A hemodynamic study of pulmonary hypertension in sickle cell disease. *N Engl J Med* 2011;365:44–53.
78. Klings ES, Anton Bland D, Rosenman D, Princeton S, Odhiambo A, Li G, Bernard SA, Steinberg MH, Farber HW. Pulmonary arterial hypertension and left-sided heart disease in sickle cell disease: clinical characteristics and association with soluble adhesion molecule expression. *Am J Hematol* 2008;83:547–553.
79. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT, *et al.* Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991;115:343–349.
80. Mehari A, Gladwin MT, Tian X, Machado RF, Kato GJ. Mortality in adults with sickle cell disease and pulmonary hypertension. *JAMA* 307:1254–1256.
81. Fonseca GH, Souza R, Salemi VM, Jardim CV, Gualandro SF. Pulmonary hypertension diagnosed by right heart catheterization in sickle cell disease. *Eur Respir J* 2012;39:112–118.
82. Machado RF, Barst RJ, Yovetich NA, Hassell KL, Kato GJ, Gordeuk VR, Gibbs JS, Little JA, Schraufnagel DE, Krishnamurti L, *et al.* Hospitalization for pain in patients with sickle cell disease treated with sildenafil for elevated TRV and low exercise capacity. *Blood* 2011;118:855–864.
83. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J* 2009;34:888–894.
84. Kovacs G, Maier R, Aberer E, Brodmann M, Scheidl S, Troster N, Hesse C, Salmhofer W, Graninger W, Gruenig E, *et al.* Borderline pulmonary arterial pressure is associated with decreased exercise capacity in scleroderma. *Am J Respir Crit Care Med* 2009;180:881–886.
85. van Beers EJ, Nur E, Schaefer-Prokop CM, Mac Gillavry MR, van Esser JW, Brandjes DP, Kappers-Klunne MC, Duits AJ, Muskiet FA, Schnog JJ, *et al.* Cardiopulmonary imaging, functional and laboratory studies in sickle cell disease associated pulmonary hypertension. *Am J Hematol* 2008;83:850–854.
86. Yung GL, Channick RN, Fedullo PF, Auger WR, Kerr KM, Jamieson SW, Kapelanski DP, Moser KM. Successful pulmonary thromboendarterectomy in two patients with sickle cell disease. *Am J Respir Crit Care Med* 1998;157:1690–1693.

87. Kato GJ, Gladwin MT. Evolution of novel small-molecule therapeutics targeting sickle cell vasculopathy. *JAMA* 2008;300:2638–2646.
88. Machado RF, Martyr S, Kato GJ, Barst RJ, Anthi A, Robinson MR, Hunter L, Coles W, Nichols J, Hunter C, *et al*. Sildenafil therapy in patients with sickle cell disease and pulmonary hypertension. *Br J Haematol* 2005;130:445–453.
89. Villagra J, Shiva S, Hunter LA, Machado RF, Gladwin MT, Kato GJ. Platelet activation in patients with sickle disease, hemolysis-associated pulmonary hypertension, and nitric oxide scavenging by cell-free hemoglobin. *Blood* 2007;110:2166–2172.
90. Derchi G, Forni GL, Formisano F, Cappellini MD, Galanello R, D'Ascola G, Bina P, Magnano C, Lamagna M. Efficacy and safety of sildenafil in the treatment of severe pulmonary hypertension in patients with hemoglobinopathies. *Haematologica* 2005;90:452–458.
91. Benza RL. Pulmonary hypertension associated with sickle cell disease: pathophysiology and rationale for treatment. *Lung* 2008;186:247–254.
92. Minniti CP, Machado RF, Coles WA, Sachdev V, Gladwin MT, Kato GJ. Endothelin receptor antagonists for pulmonary hypertension in adult patients with sickle cell disease. *Br J Haematol* 2009;147:737–743.
93. Barst RJ, Mubarak KK, Machado RF, Ataga KI, Benza RL, Castro O, Naeije R, Sood N, Swerdlow PS, Hildesheim M, *et al*. Exercise capacity and haemodynamics in patients with sickle cell disease with pulmonary hypertension treated with bosentan: results of the ASSET studies. *Br J Haematol* 2010;149:426–435.
94. Lin EE, Gladwin MT, Machado RF. Pulmonary hypertension in patients with hemoglobinopathies: could a mechanism for dysfunction provide an avenue for novel therapeutics? *Haematologica* 2005; 90:441–444.
95. Kato GJ. Novel small molecule therapeutics for sickle cell disease: nitric oxide, carbon monoxide, nitrite, and apolipoprotein A-I. *Hematology Am Soc Hematol Educ Program* 2008:186–192.
96. Sullivan KJ, Kissoon N, Sandler E, Gauger C, Froyen M, Duckworth L, Brown M, Murphy S. Effect of oral arginine supplementation on exhaled nitric oxide concentration in sickle cell anemia and acute chest syndrome. *J Pediatr Hematol Oncol* 2010;32:e249–e258.
97. Morris CR, Morris SM Jr, Hagar W, Van Warmerdam J, Claster S, Kepka-Lenhart D, Machado L, Kuypers FA, Vichinsky EP. Arginine therapy: a new treatment for pulmonary hypertension in sickle cell disease? *Am J Respir Crit Care Med* 2003;168:63–69.
98. Voskaridou E, Tsetsos G, Tsoutsias A, Spyropoulou E, Christoulas D, Terpos E. Pulmonary hypertension in patients with sickle cell/beta thalassemia: incidence and correlation with serum N-terminal pro-brain natriuretic peptide concentrations. *Haematologica* 2007;92: 738–743.
99. Kiter G, Balci YI, Ates A, Hacioglu S, Sari I. Frequency of pulmonary hypertension in asymptomatic beta-thalassemia major patients and the role of physiological parameters in evaluation. *Pediatr Hematol Oncol* 2010;27:597–607.
100. Hagar RW, Morris CR, Vichinsky EP. Pulmonary hypertension in thalassaemia major patients with normal left ventricular systolic function. *Br J Haematol* 2006;133:433–435.
101. Du ZD, Roguin N, Milgram E, Saab K, Koren A. Pulmonary hypertension in patients with thalassemia major. *Am Heart J* 1997;134:532–537.
102. Aessopos A, Farmakis D, Deftereos S, Tsironi M, Tassiopoulos S, Moyssakis I, Karagiorga M. Thalassemia heart disease: a comparative evaluation of thalassemia major and thalassemia intermedia. *Chest* 2005;127:1523–1530.
103. Aessopos A, Farmakis D, Karagiorga M, Voskaridou E, Loutradi A, Hatziliami A, Joussef J, Rombos J, Loukopoulos D. Cardiac involvement in thalassemia intermedia: a multicenter study. *Blood* 2001;97:3411–3416.
104. Atichartakarn V, Likittanasombat K, Chuncharunee S, Chandanamattha P, Worapongpaiboon S, Angchaisuksiri P, Aryurachai K. Pulmonary arterial hypertension in previously splenectomized patients with beta-thalassemic disorders. *Int J Hematol* 2003;78:139–145.
105. Schilling RF, Gangnon RE, Traver MI. Delayed adverse vascular events after splenectomy in hereditary spherocytosis. *J Thromb Haemost* 2008;6:1289–1295.
106. Zhang Y, Qui Y, Zhu J, Gao D. Pulmonary hypertension associated with autoimmune hemolytic anemia: a case report. *Int J Cardiol* 2007;115:e1–e2.
107. Connor P, Veys P, Amrolia P, Haworth S, Ashworth M, Moledina S. Pulmonary hypertension in children with Evans syndrome. *Pediatr Hematol Oncol* 2008;25:93–98.
108. Labrune P, Zittoun J, Duvaltier I, Trioche P, Marquet J, Niaudet P, Odievre M. Haemolytic uraemic syndrome and pulmonary hypertension in a patient with methionine synthase deficiency. *Eur J Pediatr* 1999;158:734–739.
109. Monsuez JJ, Auperin I, Vittecoq D, Heshmati F. Pulmonary hypertension associated with thrombotic thrombocytopaenic purpura in AIDS patients. *Eur Heart J* 1997;18:1036–1037.
110. Heller PG, Grinberg AR, Lencioni M, Molina MM, Roncoroni AJ. Pulmonary hypertension in paroxysmal nocturnal hemoglobinuria. *Chest* 1992;102:642–643.
111. Hill A, Rother RP, Wang X, Morris SM Jr, Quinn-Senger K, Kelly R, Richards SJ, Bessler M, Bell L, Hillmen P, *et al*. Effect of eculizumab on haemolysis-associated nitric oxide depletion, dyspnoea, and measures of pulmonary hypertension in patients with paroxysmal nocturnal haemoglobinuria. *Br J Haematol* 2010;149:414–425.
112. Janka JJ, Koita OA, Traore B, Traore JM, Mzayek F, Sachdev V, Wang X, Sanogo K, Sangare L, Mendelsohn L, *et al*. Increased pulmonary pressures and myocardial wall stress in children with severe malaria. *J Infect Dis* 2010;202:791–800.