Sickle Cell Disease-Associated Pulmonary Hypertension: Overview of Clinical Manifestations and Emerging Therapeutic Options

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Advances in the care of patients with sickle cell disease (SCD) and other hemolytic disorders have led to a significant improvement in their life expectancy. As this patient population ages, new chronic complications develop, and pulmonary hypertension (PH) is emerging as one of the leading causes of morbidity and mortality in adult patients with various hemolytic disorders.

SCD occurs in individuals who are homozygous for a single nucleotide substitution in the beta-globin gene, resulting in the synthesis of hemoglobin S (HbS), a structural variant much less soluble than normal hemoglobin (HbA) when deoxygenated. Deoxygenated HbS polymerizes and aggregates inside sickle erythrocytes. Rigid, dense, sickled cells become entrapped in the microcirculation, a process that is enhanced by their propensity to adhere to endothelium. Resulting ischemia and reperfusion injury promote inflammatory, thrombotic, and oxidant stress, which leads to episodes of bone pain and acute chest syndrome. The membrane of erythrocytes containing intracellular HbS polymer is exposed to cumulative mechanical injury in the microcirculation, which shortens the red cell life span. SCD is characterized by a chronic hemolytic anemia. Intravascular hemolysis releases free hemoglobin and red-cell arginase into the plasma, producing endothelial dysfunction, vascular proliferation, and pro-oxidant and proinflammatory stress. These mechanisms ultimately result in a proliferative vasculopathy affecting the brain, kidney, and lung vasculature, a hallmark of which is the development of PH in adulthood.

It is estimated that around 250,000 children worldwide are born with homozygous SCD every year.[1] Approximately 0.15% of African-Americans are homozygous for SCD, and 8% have sickle cell trait. Despite significant improvements in the life expectancy of SCD patients, estimates of the median age at death are 42 to 53 years for men and 48 to 58.5 years for women.[2,3] Pulmonary complications account for a large proportion of adult deaths.[2,4-6] According to the Cooperative Study of Sickle Cell Disease, a prospective multicenter study of 3,764 patients, more than 20% of adults had fatal pulmonary complications.[2] Among the 299 patients enrolled in the long-term follow-up study of patients who participated in the Multicenter Study of Hydroxyurea in Sickle Cell Anemia, pulmonary disease was the most common cause of mortality, accounting for 28 % of all deaths.[7] Among the chronic cardiopulmonary complications of SCD, PH has emerged as the major threat to the well-being and longevity of patients with SCD.[8, 9]

Epidemiology, Risk Factors, and Mortality

Pulmonary arterial hypertension (PAH), characterized by elevated pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR), is an increasingly recognized complication of SCD.[10-15] Echocardiographic studies performed at tertiary care SCD centers have reported that 20% to 30% of screened patients have PH.[10,14] Recent autopsy studies suggest that up to 75% of SCD patients have histological evidence of PAH at the time of death[16] (**Figure 1**). Furthermore, SCD patients with PH have a significantly increased mortality rate compared with patients without PH. Sutton and colleagues reported a 40% mortality rate at 22 months, with an odds ratio for death of 7.86 (2.63-23.4).[14] Powars and colleagues reported a mean 2.5-year survival in SCD patients with chronic lung disease with PH.[5] De Castro and colleagues[17] similarly reported a 50% 2-year mortality rate in SCD-PH patients.

These retrospective data were confirmed by the National Institutes of Health (NIH) PH screening study in patients with SCD.[18] In this prospective study, 195 adult SCD patients were screened with transthoracic Doppler echocardiograms. Tricuspid regurgitant jet velocity (TRV) was used to estimate the pulmonary artery systolic pressure (PASP). PH was prospectively defined as a TRV of 2.5 m/s or greater, and moderate-to-severe PH was defined as a TRV of 3.0 m/s or greater. Right heart catheterization was performed in patients with a TRV of 2.8 m/s or greater, and measured PASP correlated closely to that estimated by the TRV. Thirty two percent of SCD patients had a TRV of 2.5 m/s or greater and 9% had a TRV of 3.0 m/s or greater.

On univariate statistical analysis, markers of hemolytic

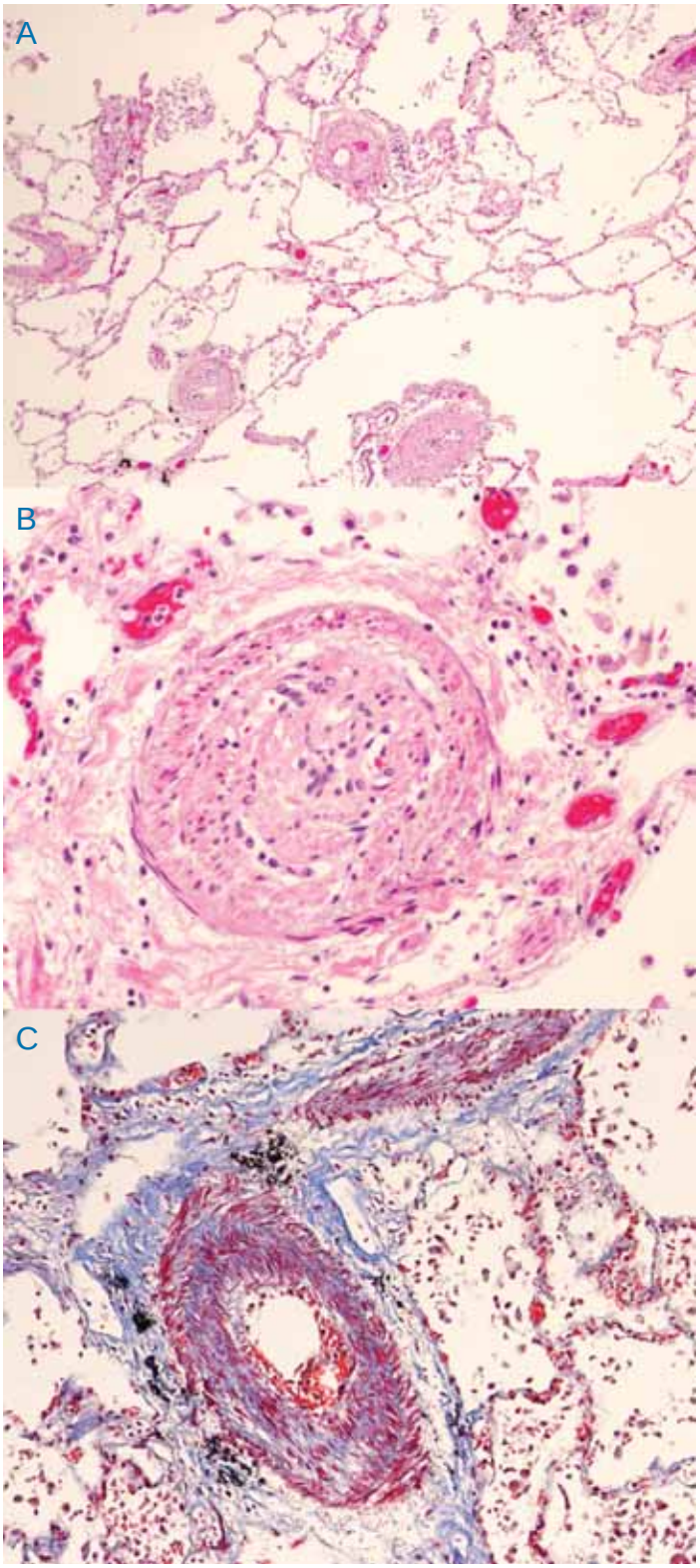

Figure 1. Pulmonary arteriopathy in sickle cell-related pulmonary hypertension. Autopsy findings of a patient with sickle cell disease and pulmonary hypertension who died suddenly during an episode of vasoocclusive crisis. Right heart catheterization performed approximately a year earlier demonstrated the following: RAP 12 mmHg, mPAP 40 mmHg, PCWP 13 mmHg, cardiac output 7.7 L/min, and PVR 281 dyn/s·cm-5. A: Low-power photomicrograph demonstrating pulmonary arterial smooth muscle hypertrophy (H & E stain). B: Plexogenic lesion (H & E stain). C: Smooth muscle cell hyperplasia (Mason trichrome stain).

anemia (low hemoglobin and hematocrit, high aspartate aminotransferase but not alanine aminotransferase, and high lactate dehydrogenase levels) were associated with elevated PASP. Increasing age was also a univariate predictor of a high TRV, and PH patients were significantly older than patients without PH. Multiple logistic regression analysis identified a history of renal or cardiovascular complications, increased systemic systolic blood pressure, elevated lactate dehydrogenase and alkaline phosphatase, and low transferrin levels as independent predictors of PH. In men, a history of priapism was an independent factor associated with PH. These associated risk factors suggest that PH represents a component of the systemic vasculopathy of SCD (characterized by systemic hypertension, renal failure, and priapism), and that it is mechanistically linked to hemolytic rate, iron overload, and cholestatic hepatic dysfunction. Interestingly, the development of PH was not associated with markers of inflammation, fetal hemoglobin levels, or platelet counts.

In another recent prospective study of 60 patients systematically sampled at a comprehensive SCD treatment center, the prevalence of PH was 30%.[19] A similar prevalence of PH was estimated for a subgroup of patients enrolled in the 1996 Multicenter Study of Hydroxyurea (MSH) in Sickle Cell Anemia Patients' Follow-up Study.[20]

In the NIH PH screening study, a TRV of at least 2.5 m/s, as compared with a velocity of less than 2.5 m/s, was independently associated with a marked increased risk of death (RR = 10.1; 95%CI = 2.2-47; $P < .001$). The 18-month mortality was 16% for patients with a TRV of 2.5 m/s or greater and was less than 2% in patients without PH. Follow-up data from this cohort continue to be updated and demonstrate that PH remains a strong independent risk factor for death, with a 45-month mortality rate of approximately 40%. From current Cox regression analysis, the estimated risk ratio of death, relative to patients with a TRV of less than 2.5 m/s, is 4.4 (95%CI = 1.6-12.2; $P < .001$) for patients with a TRV of 2.5-3.0 m/s and 10.6 (95%CI = 3.3-33.6; $P < .001$) for patients with a TRV greater than 3.0 m/s (**Figure 2**). In addition, a study by Castro and colleagues reported a similar prevalence of PH (36% in patient with HbSS and S-beta^0 thalassemia and 25% in SC and S-beta$^+$ thalassemia) and a remarkably similar 17% mortality rate for patients with PH over 2 years compared with approximately 2% for subjects without PH.[21] Ataga and colleagues have also shown a 10% mortality rate for patients with PH over 26 months in comparison to 1% in those patients without PH[22] (**Table 1)**.

Two centers independently reported the follow-up of adult SCD patients who on initial echocardiographic screening had normal TRVs. After 2 to 3 years of follow-up, 13% to 15 % of these patients developed high TRVs, suggesting a PH incidence of about 4% to 7 % per year.[22,23]

Clinical Manifestations and Diagnostic Evaluation

The diagnosis of SCD-PH can be challenging. Exertional dyspnea, the most typical presentation of PH, is also a cardinal symptom of chronic anemia, and a high index of suspicion is necessary. Other common conditions in SCD, such as left

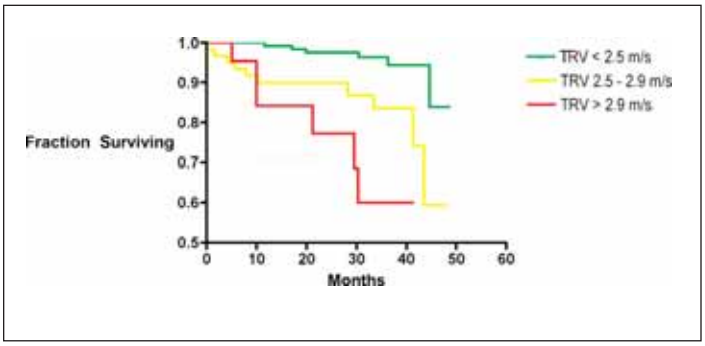

Figure 2. Kaplan–Meier survival curves according to tricuspid regurgitant jet velocity {TRV}. The survival rate is significantly higher among patients with a TRV of less than 2.5 m/s than among those with a TRV of at least 2.5 m/s (P < .001). Updated from Gladwin et al.[18]

ventricular dysfunction, pulmonary fibrosis, and liver cirrhosis, could present in a similar fashion and could also result in PH.

Diagnostic evaluation of patients with suspected SCD-PH should follow the same guidelines established for other causes of PH.[24,25]

Echocardiographic Screening

The extremely high prevalence of PH in the population and associated high mortality demand universal noninvasive screening of all adults with Doppler echocardiography (**Figure 3**). Although no prospective data on prevalence and risk are available for children, we currently recommend that children with high hemolytic rates (hemoglobin values below 7 g/dL with high lactate dehydrogenase values) and/or recurrent acute chest syndrome be screened. We have recently observed increased pulmonary pressures in SCD patients during mild exercise and vaso-occlusive painful crisis.[26] As such, it is important to perform echocardiographic screening in steady state (at least 2 weeks after a vaso-occlusive painful crisis and at least 1 month after an episode of acute chest syndrome) and we recommend the use of exercise echocardiography in patients with unexplained significant exertional dyspnea and a normal resting TRV.

Right Heart Catheterization

Right heart catheterization is strongly recommended by the authors in patients with moderate-to-severe PH (ie, a TRV greater than 2.9 m/s) on screening echocardiography (**Figure 3**). Right heart catheterization is essential to confirm the PH diagnosis, to establish the severity of the associated right ventricular dysfunction and to exactly define the hemodynamic profile of the patient.

Hemodynamically, SCD-PH is characterized by mild-to-moderate elevation in mean PAP (in the range of 30 to 40 mmHg), mild relative elevation in PVR, mild pulmonary capillary wedge pressure (PCWP) elevation and high cardiac output (**Table 2**).

Among patients with SCD-PH undergoing right heart catheterization at the NIH (Anthi et al, submitted for publication), PAH (defined as mean PAP ≥ 25 mmHg and PCWP £ 15 mmHg) was present in 54% of catheterized patients. Pulmonary venous hypertension secondary to left ventricular diastolic dysfunction (mean PAP ≥ 25 mmHg, PCWP > 15 mmHg, and mean PAP-PCWP gradient £ 12 mmHg) was present in 31% of patients. The remaining 15% of patients had PH of mixed etiology (mean PAP ≥ 25 mmHg, PCWP > 15 mmHg, and mean PAP-PCWP gradient > 12 mmHg).

These findings suggest that the etiology of PH in SCD and other hemolytic disorders is multifactorial, with half of the catheterized patients having PAH with intrinsic pulmonary arteriopathy and half having PH associated with left ventricular diastolic dysfunction. This is consistent with the observation that echocardiographic evidence of diastolic dysfunction is common in SCD patients, but contributes to PH in only one third of patients with a TRV of 2.5 m/s or greater.[27] Interestingly, echocardiographic signs of left ventricular diastolic dysfunction (evidenced by a low E/A ratio) and PH (evidenced by an elevated TRV) are independent and additive risk factors for death in the NIH PH screening study cohort.[27]

It is important to emphasize that PH in patients with hemolytic diseases is clearly a disorder that is different from other forms of PAH. Presence of chronic anemia requires a high resting cardiac output (usually around 10 L/min) to compensate for a decrease in the blood oxygen carrying capacity. It is likely that in patients with critical anemia, any degree of PH is poorly tolerated and results in significant morbidity and possibly mortality. Consistent with this hypothesis are the results of a recently presented study evaluating the cardiopulmonary function of patients with SCD[28] (and of Anthi et al, submitted for publication). When compared with age, gender, and hemoglobin-matched patients who had SCD without PH, patients with PH and a mean PAP ? 36 mmHg exhibited a lower 6-minute walk test (6MWT) distance (435 ± 31 vs 320 ± 20 meters; *P* = .002) and peak oxygen consumption on cardiopulmonary exercise testing (50 ± 3% versus 41 ± 2% of predicted; *P* = .02). In comparison, in a randomized trial evaluating the effects of the selective endothelin antagonist sitaxsentan in patients with PAH with a mean PAP of 54 mmHg, the mean baseline 6MWT distance was 398 meters and the mean peak oxygen consumption was 46% of predicted.[29] Taken together, these data suggest that in patients with chronic anemia, mild-to-moderate PH has a severe adverse impact on functional and aerobic exercise capacity.

Symptom Evaluation and Functional Assessment

The most commonly utilized test to evaluate functional capacity in patients with PH is the 6MWT. While the 6MWT has not been extensively validated in patients with hemolytic disorders, we have presented preliminary data in patients with SCD demonstrating that the 6MWT distance directly correlates with peak oxygen consumption and inversely with the degree of PH.[26] Furthermore, 6MWT distance improves with therapy, suggesting that the test could be used in this patient population.[30] A recent study of sildenafil in patients with thalassemia also demonstrates improvement in 6MWT distance.[31]

Laboratory Tests

Minimally required tests to rule out other associated etiologies would include serologic testing for collagen vascular disorders, HIV, and liver function testing. The severity of iron-overload and hemolytic anemia should be assessed. We have recently validated the use of N-terminal pro-B-type natriuretic peptide (NT-proBNP) as a PH biomarker for the diagnosis and risk stratification in patients with SCD.[20] NT-proBNP levels were measured in 230 participants in the NIH PH Screening Study and in 121 samples from patients enrolled, starting in 1996, in the MSH Patients' Follow-up Study. NT-proBNP levels were higher in patients with SCD-PH and correlated directly with PH severity and the degree of functional impairment in the NIH cohort. An NT-proBNP level of 160 pg/mL or greater had a 78% positive predictive value for the diagnosis of PH and was an independent predictor of mortality (risk ratio = 5.1; 95%CI = 2.1-12.5; $P < .001$). In the MSH cohort, 30% of patients had an NT-proBNP level of ?160 pg/mL or greater, which was independently associated with mortality by Cox proportional hazards regression analysis (risk ratio = 2.87; 95%CI = 1.2-6.6; $P = .02$).

Table 1. Prevalence and Prognosis of Pulmonary Hypertension (PH) in Sickle Cell Disease.

	Studies			
	Gladwin et al[18]	**De Castro et al[21]**	**Ataga et al[22]**	**Machado et al[20]**
N	195	124	76	121
Prevalence of PH (%)	32	32	34	30
Mortality in PH patients	40% at 45 months	17% at 24 months	10% at 26 months	50% at 60 months
Mortality in patients without PH	2% at 45 months	2% at 24 months	1% at 26 months	15% at 60 months

Pulmonary Function Testing (PFT)

Pulmonary function testing will exclude or identify the presence of airflow obstruction or pulmonary parenchymal disease that could potentially exacerbate hypoxemia-associated PH. Most patients with SCD develop airflow obstruction, restrictive lung disease, abnormal diffusing capacity, and hypoxemia.[5,32-36]

Ventilation-Perfusion Lung Scintigraphy

Ventilation-perfusion (V/Q) scanning is an indispensable component of the evaluation because chronic thromboembolic pulmonary hypertension (CTEPH) is a potential curable cause of PH. This is particularly important in SCD patients, in whom thromboembolism is a documented cause of mortality. CTEPH can occur in SCD patients and has been treated surgically with success.[37] If the noninvasive imaging studies are suggestive of CTEPH, patients should undergo pulmonary angiography.

Screening Overnight Oximetry

Sleep disordered breathing with episodes of nighttime desaturation can lead to PH development, and overnight oximetry can provide the first diagnostic clue. Nighttime oxygen desaturation is a well-documented entity in children and adolescents with SCD.[38-40] Nocturnal hypoxemia contributes to the development of neurologic events and vaso-occlusive crisis through mechanisms involving upregulation of several cell-adhesion mediators.[39, 41, 42] These effects

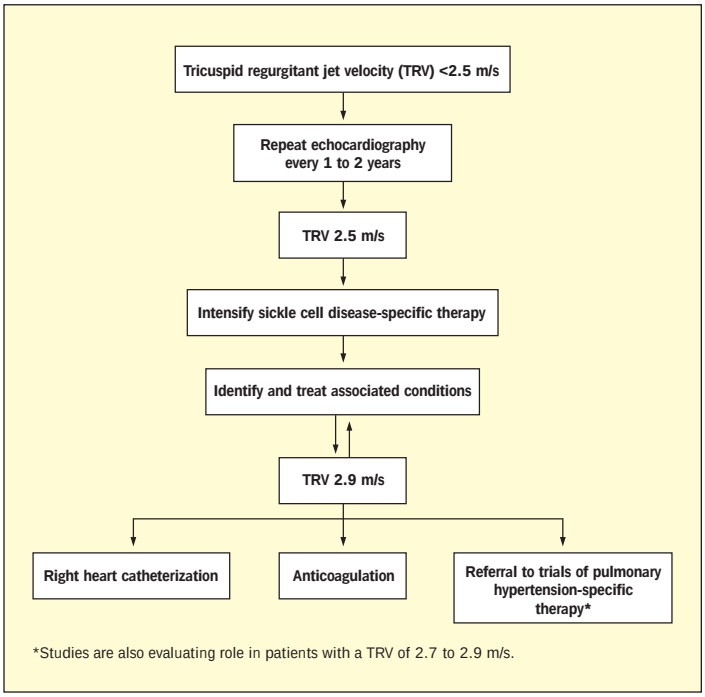

Figure 3. Treatment algorithm.

Table 2. Hemodynamic Profiles in Patients with Sickle Cell Disease.

	Without Pulmonary Hypertension	**With Pulmonary Hypertension**
PA mean (mm Hg)	19 ± 0.7	36 ± 1
Right atrial pressure (mm Hg)*	6 ± 0.4	10 ± 1
Pulmonary cappilary wedge pressure (mm Hg)	11 ± 0.5	17 ± 1
Cardiac output (L/min)	10 ± 0.5	9 ± 0.3
Pulmonary vascular resistance (dyn/sec·cm^{-5})*	59 ± 6	197 ± 14

Adapted from Castro et al,[17] Gladwin et al,[18] and Leight et al.[55]
*Not reported by Castro et al.

could also play a role in the development of the PH-associated vasculopathy.

Treatment

There are limited data on the specific management of patients with SCD-PH. Most of the recommendations are based on expert opinion or extrapolated from data derived from other forms of PAH. Our general approach usually includes maximization of SCD-specific therapy (ie, treatment of primary hemoglobinopathy), treatment of associated cardiopulmonary conditions and targeted therapy with pulmonary vasodilator and antiremodeling agents (**Figure 3**).

Intensification of Sickle Cell Disease Therapy

In SCD, the role of chronic intravascular hemolysis as a central mechanism in the PH development is supported by a correlation between markers of increased hemolytic rate and severity of PH. It is likely that optimizing SCD therapy would be beneficial through amelioration of the principal mechanism involved in PH pathogenesis. We recommend that all patients with SCD-PH undergo maximization of therapy with hydroxyurea or simple/exchange transfusions.

Hydroxyurea has been shown to decrease the incidence of pain episodes and acute chest syndrome, to reduce the need for transfusions, and to lower overall mortality.[7,43] It is possible that some of the decreases in pulmonary and cardiovascular deaths seen in hydroxyurea-treated patients could be related to an improvement in PH. However, these considerations have to be balanced with the lack of association between fetal hemoglobin levels and the use of hydroxyurea, and protection against the development of PH in our cohort study.[18] Long-term transfusion therapy in SCD patients reduces the proportion of sickle cells in the blood, thus avoiding their pathologic effects. Transfusions lower the risks of most complications of the disease, including the risks of pulmonary events and central nervous system vasculopathy.[44-46] It is also possible that exchange transfusion, targeted to a hemoglobin level of 8 to10 g/dL and an HbS level of less than 40%, might improve cardiopulmonary function and prevent PH progression. This thesis is supported by a recent report by Aessopos and colleagues showing that in well-transfused, iron-chelated patients with thalassemia major, PH was completely prevented.[47] Even if transfusion therapy does not lower hemolytic rates sufficiently to inhibit the development of vasculopathy, a higher hemoglobin level and higher oxygen-carrying capacity are likely to reduce morbidity and possibly mortality by prevention of comorbid events.

Treatment of Associated Conditions

An aggressive search for associated conditions such as iron overload, chronic liver disease, HIV infection, nocturnal hypoxemia, and thromboembolic disorders should always be undertaken given the availability of specific therapies. The possibility of oxygen desaturation, especially unrecognized nocturnal hypoxemia should be investigated.[39,41,42]

There is evidence of a beneficial effect of warfarin anticoagulation on mortality in patients with idiopathic PAH.[48-50] The potential benefits of warfarin therapy observed in idiopathic PAH have to be weighed against the risk of hemorrhagic stroke in adults with SCD. We believe that the relatively low risk of hemorrhagic stroke compared with the high risk of death in patients with severe PH supports anticoagulation in patients without a specific contraindication.

Specific Therapy for Pulmonary Hypertension

There are no long-term data on the specific PH treatment in SCD. The choice of agents is largely empirical, based on the drug safety profile and physician preference, but there are specific treatment concerns in patients with hemolytic diseases.

The systemic use of prostanoids produces significant systemic vasodilation and increases the cardiac output, raising the concern for the potential development of high-output heart failure. The risk of chronic intravenous-line related complications such as thrombosis and sepsis is likely higher in patients with SCD. The main toxicity of endothelin-1 receptor antagonists is hepatocellular injury, which could limit their applicability in patients with SCD at risk for liver dysfunction (eg, iron overload, hepatitis C). Another class effect of these agents is a dose-related decrease in hemoglobin levels usually in the range of 1 g/dL. The main concern related to the use of sildenafil is the potential development of priapism in men with SCD.

Since alterations in nitric oxide (NO) bioavailability are likely to be involved in the pathogenesis of SCD-PH, therapeutic interventions that enhance NO effects, such as inhaled NO, L-arginine, and sildenafil, may be of potential benefit. Chronic inhaled NO could be beneficial because of its ability to selectively dilate the pulmonary vasculature as well as oxidatively inactivate circulating plasma hemoglobin.[51] However, the use of chronic inhaled NO is investigational, potentially expensive, and requires relatively complicated delivery systems.[52] L-arginine is the nitrogen donor for the synthesis of NO by NO-synthase. When given for 5 to 10 days to SCD patients and moderate-to-severe PH, L-arginine (0.1 g/kg three times daily) decreased estimated PASP by a mean of 15.2%, suggesting that it may have a role in the chronic treatment of SCD-PH.[53] In a recently published case series,[31] seven patients with thalassemia intermedia, thalassemia major, or sickle thalassemia, and mean tricuspid regurgitant gradients of 45 mmHg or greater at rest, were treated with sildenafil for from 4 weeks to 48 months. Tricuspid gradient decreased in all patients and functional status as defined by New York Heart Association class and 6MWT improved. Sildenafil use resulted in symptomatic improvement and near normalization of pulmonary pressures in one patient with thalassemia intermedia.[54] We have recently reported our experience with sildenafil in patients with SCD-PH.[30] We treated 12 patients with a mean estimated PASP of 51 mmHg (mean TRV = 3.1 m/s) for a mean of 6 months. Sildenafil therapy was associated with a 10 mmHg decrease in estimated PASP, a 78 meter improvement in 6MWT distance, and decreased mean NT-proBNP by 448 pg/mL.

Based on the lack of data from long-term or placebo-controlled studies we cannot recommend any specific agent and the choice of regimen should be individualized to each

patient. In addition, practitioners should strongly consider referral to centers involved in clinical trials evaluating the effects of these agents in SCD. Careful monitoring for unanticipated adverse effects unique to this population is necessary. Two multicenter, randomized placebo-controlled trials for SCD-PH have begun or are at the final stages of planning: a trial of bosentan (ASSET-1, ASSET-2, and ASSET-3) and a National Heart, Lung, and Blood Institute-sponsored trial of sildenafil.

Conclusions and Future Directions

PH is a common complication of adults with SCD (and other chronic hemolytic disorders) associated with high morbidity and mortality. Echocardiographic screening for the presence of PH should be carried out yearly in the adult SCD patient population. It is likely that intensification of SCD-specific therapy limits the progression of the disease at early stages and may reduce associated morbidity and mortality at later stages. In patients with more severe PH, strong consideration should be given to patient referral to specialized centers for full PH work-up (including right heart catheterization) and specific therapy with vasodilators and antiremodeling agents.

Further studies are necessary to fully understand the biology of PH in patients with hemolytic disorders, such as the effects of mild elevations in pulmonary pressures on the cardiopulmonary function, mechanisms of increased mortality, and the contribution of the left ventricle to the elevations in PAP. Finally, large randomized trials evaluating the effects of specific PAH therapy in patients with SCD are under way and will help elucidate the role of these agents in this patient population. PH

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