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Pulmonary Hypertension Associated with Chronic Hemolytic Anemia and Other Blood Disorders

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INTRODUCTION

Pulmonary hypertension (PH) has emerged as a major complication of several hematologic disorders. Here the authors review the clinical manifestations, epidemiology, pathophysiology, and treatment of PH-complicating disorders of the hematologic system.

HEMOGLOBINOPATHIES

The oxygen-carrying capacity of erythrocytes relies, in part, on the presence of functional hemoglobin. The normal hemoglobin molecule, hemoglobin A (HbA), is typically comprised of 2 α -globin subunits and 2 β -globin subunits. Genetic defects may produce abnormal subunits/dysfunctional proteins or lower levels of normal hemoglobins. In addition to the specific defects associated with the different hemoglobinopathies, anemia should also be considered in the evaluation of PH in patients with these diseases. The signs and symptoms induced by anemia depend on the degree of anemia, the rate at which it evolves, the oxygen demands of patients, and the presence of chronic cardiopulmonary disease.^{1–3} From the hemodynamic standpoint, as the hemoglobin level decreases (particularly with hemoglobin values less than 7 g/dL), blood viscosity decreases, cardiac output increases, filling pressures tend to decrease, and systemic and pulmonary vascular resistances decrease substantially. Such abnormalities are readily reversible with red blood cell transfusions.^{2–4}

Sickle Cell Disease

Sickle cell disease (SCD) is one of the most common monogenetic diseases in the world. Sickle cell anemia, the most common and most severe form of SCD, occurs in individuals who are homozygous for a single nucleotide change from thymine to adenine, with the sixth

amino acid in the β -globin chain becoming valine instead of glutamic acid, resulting in the production of hemoglobin S (HbS). Other types of SCD are the result of compound heterozygotes of one copy of HbS and one copy of another β -globin mutation, such as hemoglobin SC or hemoglobin S-beta-thalassemia.⁵

Approximately 250,000 children worldwide are born with homozygous sickle cell anemia every year⁶; 0.15% of African Americans are homozygous for SCD and 8% have sickle cell trait.⁶ In sub-Saharan Africa, up to 40% of the population carry sickle cell trait and up to 1% of children are born with SCD.⁷

HbS is much less soluble than HbA when deoxygenated.^{8,9} Deoxygenated HbS polymerizes and aggregates inside sickle erythrocytes and as they traverse the microcirculation these rigid, dense and sickled cells become entrapped in the microcirculation. This process is also enhanced by inflammation and integrin molecule expression, causing red cell and leukocyte adhesion to the endothelium. These episodes of microvascular occlusion result in an interruption in blood flow, ischemia, and reperfusion injury, with secondary inflammatory, thrombotic, and oxidant stress.^{10–17} SCD is characterized by a chronic hemolytic anemia. Intravascular hemolysis releases cell-free hemoglobin into the plasma, which scavenges nitric oxide (NO), and releases red blood cell arginase-1 into the plasma, which catabolizes arginine, the substrate for NO synthesis,^{18–20} and ultimately produces a state of endothelial dysfunction, vascular proliferation, and pro-oxidant and proinflammatory stress.^{21–23}

Among the chronic cardiopulmonary complications of SCD, PH has emerged as a major cause of morbidity and mortality. A great deal of recent data has significantly added to the understanding of the prevalence, mechanisms, and clinical characterization of PH in patients with SCD. Retrospective and prospective cohort studies using Doppler echocardiography have reported that 20% to 30% of patients with SCD have an elevated estimated pulmonary artery systolic pressure that is 2 standard deviations more than the normal mean value (tricuspid regurgitant jet velocity [TRV] 2.5 m/s), whereas approximately 8% to 10% of patients have values 3 standard deviations more than the population normal mean (TRV 3.0 m/s).^{21,24–27} Further, the measurement of N-terminal pro brain natriuretic peptide (NT-proBNP) in stored plasma samples showed that 30% of individuals enrolled in the Multicenter Study of Hydroxyurea in 1996 had elevated levels, suggesting the presence of elevated pulmonary pressures and strain in the right side of the heart.²⁸ Similarly, in the Cooperative Study of Sickle Cell Disease from 1978 and 1988, 27.6% of adults had elevated levels of NT-proBNP.²⁹ In both studies, elevated study entry levels of NT-proBNP were independently associated with a higher risk of death.

Three recent studies using the gold standard diagnostic test for the disease, right heart catheterization (RHC), have provided new insights into PH in SCD (Table 1). The National Institutes of Health (NIH) screening study has followed 533 patients for a median follow-up of 4.4 years.³¹ Using preestablished inclusion criteria, 86 patients underwent RHC, of which 56 were diagnosed with PH (10.5% of the total study population). Similar findings were observed in a study of 80 patients with SCD in Brazil, which revealed a 10% prevalence of PH.²⁶ In a study of 398 patients with SCD in France, Parent and colleagues²⁷ observed a 6% prevalence of PH. Differences in the study design could explain discrepancies in the PH prevalence between the French study and both the US and Brazilian studies. Parent and colleagues²⁷ excluded approximately 10% of screened patients, including those with severe renal (creatinine clearance of less than 30 mL/min), liver (international normalized ratio >1.7), or lung disease (total lung capacity of less than 70% predicted).

The epidemiologic risk factors associated with an elevated TRV and PH documented by RHC include a history of renal or cardiovascular complications; increased systemic systolic

blood pressure; abnormalities in markers of hemolytic anemia (anemia, reticulocytosis, increased lactate dehydrogenase, aspartate aminotransferase, and bilirubin); iron overload; cholestatic liver dysfunction (elevations in alkaline phosphatase); renal insufficiency; a history of cutaneous leg ulceration; and, in men, a history of priapism.^{21,26,28,31–33} The development of and elevated TRV and PH was not associated with the number of vasoocclusive episodes or acute chest syndrome, markers of inflammation, fetal hemoglobin levels, or platelet counts.^{21,26,28,31–33} These data provide support to the hypothesis that PH arises secondary to chronic hemolytic anemia and end-organ dysfunction (renal and liver disease) rather than secondary to episodes of acute chest syndrome and related pulmonary fibrosis.

An elevated estimated pulmonary artery systolic pressure by Doppler echocardiographic screening is a significant risk factor for death in patients with SCD. In the NIH study, 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% confidence interval [CI] 1.6–12.2) and 10.6 (95% CI 3.3–33.6), respectively.²¹ De Castro and colleagues²⁵ also found that 6 of 42 patients (14%) with an elevated TRV and 2 of 83 patients (2%) with normal TRV died during a 2-year follow-up period.²⁵ Similarly, in the study by Ataga and colleagues,²⁴ 9 of 36 patients with an elevated TRV and 1 of 57 patients with normal TRV died during the 2.5-year follow-up period (relative risk 9.24 [95% CI 1.2–73.3]). In both the French and Brazilian screening studies, most of the deaths occurred in patients with TRV values greater than 2.5 m/s.

The presence of PH documented by RHC is a major risk factor for death in patients with SCD. Castro and colleagues³⁰ reported a 50% 2-year mortality rate in patients with SCD with PH, and each increase of 10 mm Hg in mean pulmonary artery pressure (PAP) was associated with a 1.7-fold increase in the rate of death (95% CI, 1.1–2.7). In the NIH study, the mortality rate was significantly higher in the PH group overall (20 deaths, 36%) than either the group without PH by RHC (3 deaths, 10%) or the general sickle cell group with normal Doppler echocardiographic estimates of pulmonary artery systolic pressure (50 deaths, 13%).³¹ In both the Brazilian²⁶ and French²⁷ cohorts, the mortality rate was significantly higher in the PH group (38% and 23%, respectively).

Mehari and colleagues³² analyzed specific hemodynamic predictors of mortality in the NIH cohort. Hemodynamic variables independently associated with mortality included mean PAP (hazard ratio [HR] 1.61, 95% CI 1.05–2.45 per 10 mm Hg increase), diastolic PAP (HR 1.83, 95% CI 1.09–3.08 per 10 mm Hg increase), diastolic PAP–pulmonary capillary wedge pressure (HR 2.19, 95% CI 1.23–3.89 per 10 mm Hg increase), transpulmonary gradient (HR 1.78, 95% CI 1.14–2.79 per 10 mm Hg increase), and pulmonary vascular resistance (HR 1.44, 95% CI 1.09–1.89 per Wood unit increase). These data suggest that mortality in adults with SCD and PH is proportional to the severity of precapillary PH.

An association between the development of PH and the intensity of hemolytic anemia has been observed in prospective screening studies of patients with SCD.^{21,24,25,27,31,33–38} Although this hypothesis has been challenged in editorials and commentaries,^{39,40} there is strong clinical and experimental evidence suggesting that hemolysis is related mechanistically to PH. Hemolysis releases plasma-free hemoglobin that inactivates the intrinsic vasodilator NO^{19,20} and arginase-1, which depletes L-arginine, the substrate for NO synthesis.¹⁸ The result of these combined pathologic processes is a state of decreased NO bioavailability and resistance to NO-dependent vasodilation.²⁰

There is a correlation between the rate of hemolysis and the levels of procoagulant factors in blood in patients with SCD^{41–43} and hemolysis; decreased NO bioavailability induces

platelet activation,⁴⁴ thrombin generation, and tissue factor activation.⁴⁵ Hemolysis is also associated with the formation of red blood cell microvesicles expressing phosphatidyl serine, which activate tissue factor.^{43,46}

Splenectomy has been reported to be a risk factor for the development of PH,⁴⁷ particularly in patients with hemolytic disorders.^{48–50} Thus, functional or surgical asplenia could also contribute to the development of PH in patients with SCD. Loss of splenic function may trigger platelet activation, promoting pulmonary microthrombosis and red cell adhesion to the endothelium.⁵¹ In addition, patients with SCD have increased levels of cell-free hemoglobin and red cell prothrombotic microvesicles; following splenectomy, the rate of intravascular hemolysis increases.⁴³

In patients with SCD, both at steady state and during vasoocclusive pain crises, plasma endothelin-1 levels are increased.⁵² In vitro, sickle erythrocytes increase endothelin-1 production by cultured human endothelial cells. In addition, endothelin receptor A antagonism abolishes the vasoconstrictive effects of media from pulmonary endothelial cells exposed to sickled erythrocytes on aortic rings.⁵² Finally, a high PAP could also result from the high-cardiac-output state associated with chronic anemia. It is possible that a high-cardiac-output state combined with hemolytic anemia and other risk factors, such as renal insufficiency and iron overload, act synergistically to cause pathologic pulmonary vascular remodeling.

The diagnostic evaluation of patients with SCD suspected of having PH should follow the same guidelines established for other causes of PH.^{53,54} Given the high prevalence of PH in this population and the associated high mortality, the authors recommend noninvasive screening of all symptomatic adults with Doppler echocardiography and assessment of steady state plasma NT-proBNP levels and functional capacity. It is important that such screening be performed in the steady state because pulmonary pressures increase during vasoocclusive painful crisis and acute chest syndrome.^{55,56} An elevated TRV cannot be used to diagnose PH. For example, only 25% of patients with a TRV of 2.5 m/s or more will actually have PH at RHC.²⁹ A TRV of 2.9 m/s or more has a higher positive predictive value of 64% but a very high false-negative rate of 42%.²⁷ The measurement of NT-proBNP levels can be used to suggest PH or for risk stratification in patients with SCD²⁸ because plasma levels are higher in patients with sickle cell PH and correlate directly with the severity of the PH and the degree of functional impairment. An NT-proBNP level of 160 pg/mL or more is also an independent predictor of mortality (risk ratio 5.1, 95% CI 2.1–12.5). Combining a TRV of 2.5 m/s or more, a high NT-proBNP level (>164.5 pg/mL) and a low 6-minute walk distance of less than 333 m, the positive predictive value for PH was 62%, with a false-negative rate of 7%.²⁷ However, as in other diseases associated with PH, RHC is absolutely necessary to confirm the diagnosis and to determine its cause in these patients.

Most adult patients with SCD develop abnormal pulmonary function characterized by mild restrictive lung disease, abnormal diffusing capacity, and radiographic signs of mild pulmonary fibrosis^{57–62}; the severity of these defects seems slightly greater in patients with PH.⁶³ In aggregate, however, the degree of pulmonary function abnormalities in these patients is rarely severe enough to be a major contributor to the cause of PH. Evidence suggestive of chronic thromboembolic pulmonary hypertension (CTEPH) occurs in approximately 5% of patients with SCD with PH⁶³; this entity has been successfully treated surgically in at least 2 such patients.⁶⁴

In studies of patients with SCD undergoing RHC, the mean cardiac output and pulmonary vascular resistance for patients without PH were 10 L/min and 59 dyn/s/cm⁵, respectively.^{3,30,63} It is within the context of these data that one must consider the impact of

PH and an elevated pulmonary vascular resistance in patients who are chronically anemic with hemolytic disorders. In patients with SCD and PH, the degree of elevation in mean pulmonary pressures is mild to moderate (30–40 mm Hg), with mild elevations in pulmonary vascular resistance.^{3,26,27,30,31,63} RHC data from these studies show that the hemodynamic cause of the PH in patients with SCD is multifactorial: pre-capillary PH (defined by a mean PAP $\geq$ 25 mm Hg and a wedge pressure $\leq$ 15 mm Hg) is present in 50% of catheterized patients, whereas pulmonary venous hypertension (postcapillary PH) secondary to left ventricular dysfunction (defined by a mean PAP $\geq$ 25 mm Hg, a wedge pressure $>$ 15 mm Hg) is present in 50%.^{3,26,27,30,31,63} An echocardiographic study of a cohort of 141 patients with SCD found that 47% of them had a high TRV, diastolic dysfunction, or both (29% had a high TRV alone, 11% had diastolic dysfunction and a high TRV, and 7% had diastolic dysfunction alone). An elevated TRV and diastolic dysfunction were associated with a relative risk of death of 5.1 (95% CI 2.0–13.3) and 4.8 (95% CI 1.9–12.1), respectively, whereas the relative risk of death when both were present was 12.0 (95% CI 3.8–38.1).⁶⁵ In addition, in a series of 483 patients with homozygous SCD, markers of diastolic dysfunction were independently associated with a low 6-minute-walk distance.³³

From a functional standpoint, patients with SCD are impaired by mild increases in PAP and pulmonary vascular resistance. When compared with age-, gender-, and hemoglobin-matched patients with SCD without PH, individuals with pulmonary hypertension exhibit lower 6-minute walk distance (435 ± 31 m vs 320 ± 20 m) and peak oxygen consumption ($50\% \pm 3\%$ vs $41\% \pm 2\%$ of predicted) and higher ventilatory equivalent for carbon dioxide at the anaerobic threshold ($31.6\% \pm 1.5\%$ vs $39.2\% \pm 1.6\%$).⁶³ The 6-minute walk distance is inversely correlated with pulmonary vascular resistance and mean PAP and directly correlated with maximal oxygen consumption, supporting the contribution of increasing PAP to the loss of exercise capacity. PAP and pulmonary vascular resistance sharply increase with exercise, suggesting that pulmonary vascular disease contributes to functional limitation in these patients.⁵⁵ In addition, a lower exercise capacity (assessed by the 6-minute walk test) in patients with PH has also been demonstrated in larger cohorts of patients with SCD.^{26,27,31,33}

There are very limited data on the specific management of patients with SCD and PH. Although this has not been tested in randomized trials of patients with SCD and PH, a reasonable approach should include maximization of SCD-specific therapy (ie, treatment of primary hemoglobinopathy with hydroxyurea or transfusion therapy according to published treatment guidelines^{66,67}), treatment of hypoxia with chronic oxygen therapy, and treatment of associated cardiopulmonary conditions (such as iron overload, chronic liver disease, human immunodeficiency virus infection, nocturnal hypoxemia, thromboembolic disorders, and left ventricular disease). In patients with SCD with pulmonary arterial hypertension (PAH) (mean PAP $\geq$ 25 mm Hg and wedge pressures $<$ 15 mm Hg, with a relatively high pulmonary vascular resistance [eg, $>$ 160 dyn/cm⁵]), PAH-specific therapy can be considered. In addition, there are no randomized controlled trials (RCT) demonstrating the benefit of any PAH-specific therapy in SCD-associated PAH. Therapy should only be initiated and monitored by a team comprised of a PAH specialist and a hematologist specializing in SCD care.

In a series of 7 patients with either thalassemia or sickle thalassemia and PH treatment with sildenafil from 4 weeks to 48 months resulted in an improvement in TRV, New York Heart Association functional class, and 6-minute walk distance.⁶⁸ In another case series, 12 patients with SCD were treated with sildenafil for a mean of 6 months with improvements in estimated pulmonary artery systolic pressure, 6-minute walk distance, and NT-proBNP levels.⁶⁹ However, these preliminary data were not supported by the results of the Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Therapy (Walk-PHaSST)

study.⁷⁰ This 16-week, NIH-sponsored multicenter, double-blind, placebo-controlled trial of sildenafil in patients with SCD with increased TRV and a low exercise capacity was stopped early, before enrollment of the planned 132 patients, because of a higher incidence of serious adverse events in the sildenafil arm (45% of sildenafil, 22% placebo, $P = .022$). Hospitalization for vasoocclusive pain crisis was the predominant cause for this difference: 35% sildenafil versus 14% placebo ($P = .029$). Importantly, there was no signal of a treatment effect on the 6-minute walk distance or NT-proBNP in the 74 patients enrolled in the study at the time of suspension. Based on these findings, phosphodiesterase type 5 inhibitors should not be used as first-line agents in patients with SCD and PAH.

Minniti and colleagues⁷¹ reported on the use of bosentan and ambrisentan (either as monotherapy or in combination with sildenafil) in a cohort of 14 patients with SCD and PH documented by RHC; with this treatment, there was a modest improvement in the 6-minute walk distance, NT-proBNP levels, and estimated pulmonary artery systolic pressure. The ASSET-1 (Assessment in Patients with Sickle Cell Disease of the Efficacy and Safety of Bosentan Therapy on Pulmonary Arterial Hypertension) and ASSET-2 studies enrolled patients with pulmonary arterial hypertension and pulmonary venous hypertension, respectively, who were randomized to bosentan or placebo. After the enrollment of 26 patients, the studies were terminated because of slow site activation and withdrawal of support by the sponsor. In this small number of patients, bosentan was well tolerated, with no significant differences in serious adverse events or laboratory tests between patients receiving the study drug; however, there was no evidence of a beneficial effect with treatment.⁷² Acute administration of epoprostenol decreases PAP and pulmonary vascular resistance and increases cardiac output in patients with PH and SCD,³⁰ but chronic therapy with these agents has not been described in the literature.

β-Thalassemia

Thalassemia refers to a spectrum of diseases characterized by reduced or absent production of one or more α- or β-globin chains. β-thalassemia is caused by impaired production of β-globin chains, which leads to a relative excess of α-globin chains.⁷³ These excess α-globin chains are unstable, incapable of forming soluble tetramers on their own, and precipitate within the cell, leading to ineffective erythropoiesis and hemolytic anemia.⁷⁴ Thalassemia major (TM), or homozygous β-thalassemia, is a severe disorder caused by the inheritance of 2 β-thalassemia alleles. Patients with this disorder develop severe and lifelong transfusion-dependent anemia, hepatosplenomegaly, and skeletal deformities caused by bone marrow expansion; they are prone to infection and skeletal fractures. β-thalassemia intermedia (TI), an entity of intermediate severity, occurs in patients with heterozygotes of 2 thalassemic variants; these patients may have skeletal abnormalities and hepatosplenomegaly similar to those seen in TM, but they usually have milder anemia. The development of PH in patients with thalassemia is likely multifactorial, involving interactions among erythrocytes via intravascular hemolysis, platelets, the coagulation system, endothelial cells, and mediators of inflammation and vascular tone.

PH is a common finding in patients with β-thalassemia; the prevalence, however, is variable, depending on the method used for screening and the type of thalassemia (**Table 2**). In most studies, the prevalence has been determined by echocardiography; however, the accuracy of echocardiography in the evaluation of PH in this entity is currently unknown. In one report, 7 patients with TI and heart failure were found to have preserved left ventricular function and severe PH by RHC.⁸¹ In a larger study of 110 patients with TI,⁸² PH was suggested by echocardiography in 60% of cases. Among these patients, 6 with heart failure and preserved systolic function underwent RHC that confirmed PH.⁸² A study comparing cardiovascular involvement in 205 patients with TI and TM, the most prevalent form of the disease,

confirmed the aforementioned findings in TI⁸⁰; in contrast, in TI, the main cardiac manifestation was left ventricular dysfunction.^{76,77,80} In 2 small studies of patients with TM, the prevalence of PH suggested by echocardiography was 75% and 79%^{75,76}; however, these patients were poorly managed by current standards and had a high prevalence of left ventricular systolic dysfunction. In summary, the true prevalence of PH in patients with thalassemia is unknown and should be determined.

Given the potential prevalence of PH, especially in TI, and the increased prevalence of left heart disease in thalassemia in general, it is reasonable to suggest that transthoracic Doppler echocardiography screening be performed in these patients; but, as in other diseases associated with PH, the diagnosis must be confirmed by RHC. Moreover, because there is an increased prevalence of left-sided cardiac disease in these patients, the cause of PH can only be conclusively differentiated by RHC.

Despite its potential complications, chronic transfusion therapy in severe thalassemia has changed the clinical course of the disease and is likely to have a favorable impact in individuals with PH. The management of those patients should focus on the disease-specific therapeutic targets that arise from the diverse pathogenetic mechanisms involved. Proper transfusion therapy restores tissue oxygen delivery and suppresses the synthesis of native defective erythrocytes, presumably ameliorating hemolysis, hypercoagulability, tissue hypoxia, and volume overload. In theory, this might obviate the development of PAH in these patients.^{83,84} Combined with transfusions, iron chelation therapy prevents iron accumulation and the resulting oxidative tissue damage. This idea is supported by a report that, in well-transfused, iron-chelated patients with TM, PH was completely prevented.⁷⁸ Hydroxyurea modifies defective hemoglobin synthesis and reduces thrombocytosis, presumably decreasing hemolysis and hypercoagulability. In a recently published study of 584 patients with TI, the use of these modalities seemed protective against the development of PH.⁸⁵ However, the study was not randomized, was retrospective, and used echocardiography for the diagnosis of PH. Yet, other small studies and case reports in these patients have reported similar observations.^{86,87} Prospective RCT of the adjuvant therapies noted earlier have not been performed and are an important area for future research.

The treatment of patients with thalassemia with confirmed PAH (group 1 PH) seems reasonable according to the current PAH guidelines, but that has never been tested in an RCT; moreover, they have been routinely excluded from the major RCT of approved pulmonary vasodilators. In a recent open-label study of 10 patients with β -thalassemia and an TRV greater than 2.5 m/s on Doppler echocardiography (none of the patients underwent confirmatory RHC), treatment with sildenafil resulted in a significant decrease in tricuspid regurgitant jet velocity and improved left ventricular end systolic/diastolic volume but did not change the 6-minute walk distance.⁸⁸ There are also case reports of favorable response to bosentan⁸⁹ and epoprostenol⁹⁰ in patients with RHC-confirmed precapillary PH. Given the lack of data, an RCT of pulmonary vasodilators in these patients should be considered. Because of the potential differences in PH causes in patients with TI and TM (eg, PAH in TI, left heart disease in TM), combining phenotypes in clinical trials is not ideal and should be avoided.

RED BLOOD CELL MEMBRANE DISORDERS

Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is a progressively debilitating and life-threatening hemolytic disease caused by an acquired clonal genetic deficiency of glycosylphosphatidylinositol-linked proteins on the surface of blood cells.⁹¹ This deficiency results in complement-mediated chronic intravascular hemolysis and subsequent life-

threatening thromboembolic disease and PH. Similarly to SCD, the mechanism by which PH evolves in these patients is thought to be caused by the vascular effect of intravascular hemolysis.

There are several case reports of patients with PNH who have developed PH.^{92,93} Some of these patients have disease similar to PAH, whereas others have PH caused by thromboembolic disease (CTEPH). In the largest study,⁹⁴ 29 patients with PNH were evaluated for PH by echocardiography as well as for evidence of red cell hemolysis and NO resistance. The investigators found that 36% of the patients had elevated pulmonary artery systolic pressure (PASP), but no patient underwent confirmatory RHC. Patients with evidence of more severe hemolysis were more likely to have elevated PAP.

There are no studies of PH treatment in these patients. However, treatment with eculizumab does decrease intravascular hemolysis and might decrease the risk of the development of PH.^{94–97}

Hereditary Spherocytosis

PH has been reported in patients with hereditary spherocytosis (HS), especially following splenectomy.^{98–100} However, PH in these small studies or case reports has been only documented by echocardiography; confirmation with RHC is lacking. In the largest study, 36 patients with HS (78% with previous splenectomy) were evaluated for PH using echocardiography and NT-proBNP.¹⁰¹ In this group of patients, the investigators observed no evidence of a significantly increased risk of developing PH and certainly not to the degree reported in either thalassemia or SCD.

These findings may have implications for the understanding of the cause of PH associated with hemoglobinopathies and other hemolytic disorders. Although this has been challenged in several forums,^{39,40} there is strong evidence suggesting that hemolysis is critical for the development of vascular complications, especially PH, in these diseases with other factors, such as splenectomy being another potential contributor. As previously discussed, case reports of PH in patients with prior splenectomy and the observation that a substantial proportion of patients with thalassemia and SCD have had a prior splenectomy or have functional asplenia suggest that it is not solely the hemolysis that increases the risk of PH but that the absence of a spleen is also a contributor. However, in HS, because splenectomy effectively eliminates hemolysis, the aforementioned observations suggest it may be of greater importance in increasing the risk for the development of PH in these patients.

Hereditary Stomatocytosis

Hereditary stomatocytosis is a rare autosomal dominant red cell membrane protein disorder, characterized by plasma membrane leakage of sodium and potassium.¹⁰² Because of this membrane instability, these red cells can exhibit abnormal responses to changes in temperature and are subject to intravascular hemolysis.¹⁰³

Recent reports suggest that hereditary stomatocytosis carries a high risk of thrombotic complications, especially after splenectomy. In fact, all cases of PH reported in patients with hereditary stomatocytosis are seemingly related to thromboembolic disease,^{104–107} including one in which the patient underwent pulmonary thromboendarterectomy¹⁰⁶ and another in which the patient underwent a heart-lung transplant.¹⁰⁷

CHRONIC MYELOPROLIFERATIVE DISORDERS

Chronic myeloproliferative disorders (CMPD) include many hematopoietic disorders; some CMPD are well characterized, such as chronic myelogenous leukemia, chronic neutrophilic

leukemia, chronic eosinophilic leukemia, polycythemia vera, idiopathic myelofibrosis, and essential thrombocytosis; others are rare or poorly characterized.¹⁰⁸ Each involves a multipotent hematopoietic progenitor cell with overproduction of one or more of the formed elements of the blood without significant dysplasia; there is also a predilection to extramedullary hematopoiesis, myelofibrosis, and transformation at varying rates to acute leukemia.

The possible association of PH with CMPD has been suggested by several case reports and small case series.^{109–122} However, the exact incidence and prevalence is not currently known. On one hand, because clinical signs of PH appear at an advanced stage of disease and, in some cases, the diagnosis of CMPD is difficult to establish because of chronic hypoxemia, the prevalence of PH may be underestimated. On the other hand, the rate of PH may be overestimated because, in almost all cases, diagnosis has been made by echocardiography and not confirmed by RHC; thus, a secondary cause, such as left ventricular dysfunction or a high output state, has not been excluded.

Two distinct clinical forms of PH have been described in patients with CMPD: CTEPH and pre-capillary PH mimicking PAH (reviewed in Ref.¹²³).

CTEPH: CMPD, especially polycythemia vera and essential thrombocytosis, is often characterized by a thrombophilic state, hyperviscosity, increased white blood cell count (WBC), all of which lead to microcirculatory disturbances and a very high rate of arterial and venous thromboses. In many cases, CTEPH has been the initial manifestation of CMPD. Also, in patients with CMPD, therapeutic splenectomy causes worsening of extramedullary hematopoiesis, increased platelet counts, and increased hematocrit, all of which may increase the risk of CTEPH.

The treatment of venous thromboses in patients with polycythemia vera and essential thrombocytosis does not differ from that of other patients. As in other cases of CTEPH, pulmonary endarterectomy (PTE) is the treatment of choice in these patients. In patients who are inoperable or have PH after PTE, medical therapy including diuretics, anticoagulants, and specific PAH therapy can be considered. However, no data on specific PAH therapy exist for patients with CTEPH associated with CMPD. In patients with a high thrombotic risk, therapy with hydroxyurea is recommended.¹²⁴

Precapillary PH mimicking PAH^{73,110,120,125–137}: Several factors have been suggested for the pathogenesis of PAH in patients with CMPD: (1) Portal hypertension, which is a cause of PAH and is a well-known complication of myeloid metaplasia with myelofibrosis.¹³⁸ (2) Chemotherapeutic agents or stem cell transplantation, both of which are treatment options for these conditions and have been associated with pulmonary venoocclusive disease.¹²⁵ (3) Tumor microembolism.^{120,129} (4) Extra-medullary hematopoiesis, although rare, is often associated with several of these syndromes. Pulmonary myeloid infiltration may be related to development of PH.¹³⁹ (5) Blood cell proliferation (platelets, WBC, or red blood cell count) in patients with CMPD may contribute to the development of PH.^{73,122,136} (6) Enhanced angiogenesis in the peripheral blood and bone marrow might also be a possible link between CMPD and PH.^{130,131} (7) Drug toxicity: There are recent reports of reversible PH in patients with chronic myelogenous leukemia (CML) treated with dasatinib.¹³⁷ This PH has improved or even resolved after discontinuation of dasatinib.¹³⁷

Considering the many proposed possible links between CMPD and development of PH, many therapies have been suggested. However, there are no RCT of any of these interventions, such as cytoreductive therapy¹²⁴, hematological control¹²⁴; whole-lung, low-dose, external beam radio-therapy^{133,134,139}; anticoagulation and antiplatelet agents¹⁴⁰; and pulmonary-specific vasodilators.¹⁰⁹ All of these strategies should be studied further.

In summary, the incidence and prevalence of PH in patients with CMPD have not been defined in large prospective studies. Two distinct forms of PH have been described in patients with CMPD: CTEPH and precapillary PH mimicking PAH. PAH-like PH is usually diagnosed late in the course of CMPD, whereas CTEPH is usually diagnosed earlier. Treatment of PH associated with CMPD has not been rigorously studied, and RCT have not been performed with any of the proposed therapies. PTE, however, is the treatment of choice in eligible patients with CTEPH.

SPLENECTOMY

Splenectomy has long been recognized as a risk factor for PH.^{47,141} A recent study of 43 patients with various disorders and reasons for splenectomy found a higher occurrence of PH in these patients than in case controls; however, the diagnosis was made by echocardiography and not confirmed by RHC.¹⁴²

The exact mechanism by which PH develops after splenectomy remains unclear.¹⁴³ In thalassemia and SCD, PH has been described following splenectomy, with some studies reporting the prevalence of PH as high as 75%. Asplenia has also been reported as an independent risk factor for PH following splenectomy for HS,^{98–100} idiopathic thrombocytopenic purpura,⁴⁷ and other hemolytic disorders.^{104,105,142} There is also evidence that splenectomy can increase the risk of PH in patients who do not have hemolytic disorders, such as trauma⁴⁷ and Gaucher disease.¹⁴⁴ These observations suggest that asplenia may be a risk factor for PH regardless of the underlying condition.

Several mechanisms have been postulated for PH following splenectomy: (1) platelet and/or endothelial activation by abnormal red cells and red cell fragments with subsequent deposition of platelet-rich microthrombi in the pulmonary vasculature; and (2) decreased NO bioavailability secondary to intravascular hemolysis resulting in endothelial dysfunction and/or platelet activation.¹⁴³ Although these mechanisms may contribute to PH in SCD and thalassemia (continued intravascular hemolysis following splenectomy), they do not explain conditions such as HS (splenectomy effectively eliminates hemolysis) or trauma (no significant hemolysis). Thus, it has been proposed that splenectomized individuals have increased levels of circulating prothrombotic microparticles, which have been associated with PH.⁴¹

SUMMARY

PH complicates several hematologic disorders. The cause of PH in patients with hematologic disorders is multifactorial, and a thorough diagnostic evaluation following established guidelines for PH is essential at the individual patient level and also in large studies designed to determine disease prevalence, mechanisms, and causes. There are virtually no high-quality data on the safety and efficacy of PH-targeted therapy in this patient population, and trials of therapies in these patients are needed.

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KEY POINTS

- Pulmonary hypertension (PH) has emerged as a major complication of several hematologic disorders.
- With the exception of sickle cell disease, there are a limited number of studies evaluating the prevalence of PH using the gold standard right heart catheterization.
- The cause of the PH in patients with hematologic disorders is multifactorial.
- There are virtually no high-quality data on the safety and efficacy of PH-targeted therapy in this patient population.

Table 1

RHC-based PH screening studies in SCD

	Parent ²⁷	Fonseca ²⁶	Mehari ^{31,32}
Subjects screened (N)	398	80	531
Number of subjects with PH	24	8	55
Percent of screened population	6.0	10.0	10.5
mPAP, mm Hg	30 ± 6	33 ± 9	36 ± 9
CO, l/min	9 ± 2	5 ± 2 ^a	9 ± 2
PVR, dyns/cm ⁵	138 ± 58	179 ± 120 ^b	227 ± 149
6MWD, m	404 ± 94	460 ± 152	358 ± 115
Number of subjects with precapillary PH (% of screened population)	11 (2.7)	3 (3.75)	31 (6.0)
Number of subjects with postcapillary PH (% of screened population)	13 (3.3)	5 (6.25)	24 (4.5)
Mortality in PH/no PH group (%)	12.5/1.4	38.0/5.5	36.0/13.0

Abbreviations: 6MWD, 6-minute walk distance; CO, cardiac output; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance.

^a Cardiac index (l/min/m²).

^b Converted mean value: PVR measured in Wood units.

Table 2

PH studies in thalassemia

Study	Number of Patients	Type of Thalassemia	Criteria for PH	Prevalence of PH (%)
Grisaru et al, ⁷⁵ 1990	35	Major	ECHO: PAT/RVET	75
Du et al, ⁷⁶ 1997	33	Major	ECHO: TPG+ RAP >30 mm Hg	79
Derchi et al, ⁷⁷ 1999	130	Major	ECHO: TPG	10
Aessopos et al, ⁷⁸ 2004	202	Major	ECHO: TPG >30	10
Hagar et al, ⁷⁹ 2006	36	Major	ECHO: TRV >2.5 m/s	44
Aessopos et al, ⁸⁰ 2005	36	Major	ECHO: TPG >30	10
Aessopos et al, ⁸⁰ 2005	74	Intermedia	ECHO: TPG >30	60
Aessopos et al, ⁸¹ 1995	7	Intermedia	RHC	100
Aessopos et al, ⁸² 2001	110	Intermedia	ECHO: TPG >30 and RHC	59

Abbreviations: ECHO, echocardiography; PAT/RVET, ratio of pulmonary valve acceleration time to right ventricular ejection time; RAP, right atrial pressure; TPG, tricuspid systolic pressure gradient.