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HEMATOLOGY eDIGEST



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Program Information

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In this Issue... *Pulmonary Hypertension and Other Complications of Hemolysis in Sickle Cell Disease and Thalassemia*

A central mechanistic feature of both sickle cell disease and thalassemia is hemolytic anemia. Historically, this complication has been considered to increase only the risk for cholelithiasis and symptomatic anemia; however, more recent data suggest that intravascular hemolysis may produce a state of endothelial dysfunction and resistance to nitric oxide. This ultimately leads to smooth muscle and intimal hyperplasia, proliferative vasculopathy, and increased risk of thrombosis.

In this context, it is now increasingly apparent that both diseases, as well as other hereditary and acquired hemolytic anemias, are associated with a high incidence and prevalence of pulmonary hypertension. Indeed, pulmonary hypertension is rapidly emerging as a major cause of early mortality in sickle cell disease (and likely thalassemia). Although in a small subset of these patients cor pulmonale has been recognized for many decades, cases of mild or moderate pulmonary hypertension in most patients present few or no symptoms, yet still pose a very significant risk of early death.

Agents to treat pulmonary hypertension in this population are promising in pilot studies, with larger-scale clinical trials needed to help guide clinical practice. In patients with pulmonary hypertension due to sickle cell disease or thalassemia, the greatest experience has been gained with sildenafil, and a large clinical trial is anticipated.

The high prevalence of pulmonary hypertension in patients with thalassemia indicates that red cell sickling is unlikely to be the principal cause of pulmonary hypertension in patients with sickle cell disease. In these and other hemolytic disorders with a large intravascular component, other vascular complications such as priapism and cutaneous leg ulceration are emerging. Further, strong and consistent evidence is arising that intravascular hemolysis unleashes red cell contents into blood plasma, where they behave as chronic toxins that rob blood vessels of nitric oxide, a critical component in maintaining vascular health.

In this issue, we review the current literature on the etiology, diagnosis, and management of pulmonary hypertension in patients with hemolytic disorders.

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Commentary

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Pulmonary hypertension is rapidly emerging as potentially the most serious complication of hemoglobinopathy associated with early mortality. In adults with sickle cell disease, even mild pulmonary hypertension places patients in a group with a 40% mortality rate at 40 months from its recognition – no other form of organ dysfunction in these patients places them at such high risk for early death. Comparable data, reviewed within this issue, have now been published from Howard University, National Institutes of Health, and the University of North Carolina, Chapel Hill, and presented at the American Society of Hematology meeting from Duke Medical Center. This understanding has been arising in parallel in the thalassemia literature over the last several years, particularly in untransfused patients with thalassemia intermedia.

Clearly, clinical hematologists will need to become familiar with screening and clinical suspicion of pulmonary hypertension in patients with hemoglobinopathies. They will also need to develop clinical alliances with pulmonologists or cardiologists knowledgeable in the diagnosis and management of pulmonary hypertension. One problem arising in this alliance is that many pulmonologists and cardiologists in clinical practice may not be aware that patients with sickle cell disease cannot tolerate even mild to moderate degrees of pulmonary hypertension. It is likely that the low oxygen-carrying capacity in these anemic patients, coupled with widespread organ dysfunction and in some cases, concurrent left ventricular diastolic dysfunction, may cause patients with sickle cell disease and pulmonary hypertension to succumb long before pulmonary pressures rise to alarming levels. Although it still remains to be proven that pulmonary hypertension is a direct cause of this early mortality, it seems likely that this will be the case.

The etiology of pulmonary hypertension in these hemolytic disorders is undoubtedly multifactorial. However, impairment of nitric oxide-dependent blood flow appears to be a major factor. Intravascular hemolysis releases both hemoglobin and arginase into blood plasma, where the former scavenges nitric oxide, while the latter depletes plasma of L-arginine, the substrate for nitric oxide production by nitric oxide synthase. Compounding this, nitric oxide is consumed by reactive oxygen species produced in large amounts in patients with sickle cell disease by xanthine oxidase and NADPH oxidase. Depletion of nitric oxide thus results in a

proliferative vasculopathy with chronic vasoconstriction and increased activity of tissue factor, thrombin, endothelin-1 and endothelial adhesion molecules, accompanied by platelet activation. These mechanisms provide novel targets for therapeutic intervention, and several active agents are in clinical trials.

Therapeutic trials are needed to define the optimal treatment approach in hemolysis-associated pulmonary hypertension. Until then, in patients with a tricuspid regurgitant jet velocity of 3 m/sec or greater, we favor as a first step attempting to reduce the hemolytic rate by aggressive hydroxyurea therapy or institution of chronic monthly transfusion. If the improvement in pulmonary pressure is inadequate, addition of other FDA-approved pulmonary vasodilators may be tried; note, however, that for patients with sickle cell disease, clinical trials that demonstrate efficacy and survival advantage have not yet been performed.

The scope of complications attributable to hemolysis-associated endothelial dysfunction appears to be expanding to include other disorders that are epidemiologically linked to severity of hemolysis. These complications include priapism, leg ulceration and possibly ischemic stroke. All conceivably might be mediated by a hemolysis-associated defect in NO-dependent blood flow. Additional studies will be required to better define links between these complications and hemolysis in sickle cell disease and thalassemia, as well as the other hemolytic disorders - such as hereditary spherocytosis, paroxysmal nocturnal hemoglobinuria, and red cell enzymopathies - associated in case reports with pulmonary hypertension, priapism, and leg ulceration.

☰ Pulmonary Hypertension In Sickle Cell Disease

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Pulmonary hypertension is being increasingly recognized in patients with sickle cell disease. The echocardiographic studies published by Sutton et al reported that 30% of screened adult sickle cell anemia patients have pulmonary hypertension (systolic pulmonary artery pressures (PAP) \geq 30 mm Hg). In addition, recent autopsy studies by Haque et al suggest that up to 75% of sickle cell anemia patients have histological evidence of pulmonary arterial hypertension at the time of death. These data are consistent with the results of the NIH pulmonary hypertension screening study in sickle cell disease published by Gladwin et al. That study enrolled 195 adult sickle cell anemia patients who were screened with transthoracic Doppler-echocardiograms, with tricuspid regurgitant jet velocity (TRV) used to estimate the pulmonary artery systolic pressure. To avoid a more subjective estimation of central venous pressure in this study, pulmonary hypertension was prospectively defined by a specific tricuspid regurgitant Doppler jet velocity value (TRV) \geq 2.5 m/sec and moderate-to-severe pulmonary hypertension was defined by a TRV \geq 3.0 m/sec. Right heart catheterization was performed in consenting patients with a TRV \geq 2.8 m/sec. Using these definitions, 32% of patients with sickle cell disease had elevated pulmonary artery systolic pressures and 9% had moderately-to-severely elevated pressures. Nearly identical prevalence figures have been published by Ataga et al and were also presented by De Castro at the most recent American Society of Hematology meeting.

Regarding the development of pulmonary hypertension as a predictor of a high risk of early mortality, the Sutton study reported a 40% mortality rate at 22 months with an odds ratio for death of 7.86. Similarly, Powars et al reported a mean 2.5 year survival in sickle cell patients with chronic lung disease and pulmonary hypertension, and Castro et al found a 50% two year mortality rate in patients with sickle cell disease with pulmonary hypertension confirmed by right heart catheterization. These studies involved patients with symptomatic pulmonary hypertension.

More recent prospective studies show that even mild and asymptomatic pulmonary hypertension is associated with risk of early mortality. In the Gladwin NIH screening study, a measured TRV of 2.5 m/sec or greater was associated with a ten-fold increased risk of death, which remained significant even after adjustment for other possible risk factors by proportional hazards regression analysis. Further unpublished follow-up data from our NIH cohort continues to demonstrate that pulmonary hypertension is a strong independent risk factor for mortality (RR 7.4, 95% CI 2.4-22.6, $P < 0.001$) with 40-month mortality rate of approximately 40%. In addition, De Castro and colleagues reported a remarkably similar 17% mortality rate for patients with pulmonary hypertension over 2 years compared with approximately 2% for subjects without pulmonary hypertension. Taken together, these retrospective and prospective studies strongly support the contention that pulmonary hypertension is the greatest single risk factor facing the aging population of both sickle cell disease patients and (likely) other patients with chronic high-grade intravascular hemolysis.

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8. De Castro, L. M., et al. Pulmonary Hypertension in SS, SC and S-beta Thalassemia: Prevalence, Associated Clinical Syndromes, and Mortality. Blood 2004; 104(11):462a.

Pulmonary Hypertension In Thalassemia And Other Hemolytic Disorders

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Reports of pulmonary hypertension are also accumulating involving patients with thalassemia (in particular thalassemia intermedia, hemoglobin E-thalassemia and inadequately transfused and chelated patients with thalassemia major), paroxysmal nocturnal hemoglobinuria, hereditary spherocytosis and stomatocytosis, microangiopathic hemolytic anemias, pyruvate kinase deficiency, and possibly malaria. Additionally, certain conditions are associated with both intravascular hemolysis and risk of pulmonary hypertension, such as schistosomiasis, and iatrogenic hemolysis from mechanical heart valves, left ventricular assist devices and cardiopulmonary bypass procedures. Our group at NIH has received additional reports of patients with pulmonary hypertension associated with hemolytic anemia secondary to unstable hemoglobin variants (personal communication, H. Franklin Bunn and Thomas DeLoughery). Similarly, the retrospective studies by Grisaru et al. and Derchi et al. have demonstrated that 40-50% of patients with thalassemia intermedia, and 10-75% of patients with thalassemia major, have echocardiographic evidence of pulmonary hypertension. The two more recent studies by Aessopos et al. suggest that pulmonary hypertension may be more common in patients with thalassemia intermedia and hemoglobin E- β -thalassemia than in patients with β -thalassemia major, a condition more likely occurring because most β -thalassemia major patients receive sufficient blood transfusions to reduce ineffective erythropoiesis and hemolysis. In addition, investigating pulmonary hypertension associated with thalassemia, the work by Morris and colleagues provides evidence of a disordered arginine metabolism similar to sickle cell disease.

1.

Grisaru D, Rachmilewitz EA, Mosseri M, et al. Cardiopulmonary assessment in beta-thalassemia major. Chest 1990;98:1138-1142.



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Derchi G, Fonti A, Forni GL, et al. Pulmonary hypertension in patients with thalassemia major. Am Heart J. 1999;138:384.



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Treatment of Pulmonary Hypertension in Hemoglobinopathies

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Due to the absence of clinical guidelines and placebo-controlled therapeutic trials for the evaluation and treatment of pulmonary hypertension in the sickle cell population, our diagnostic and therapeutic approach must be summary in nature. Because it is not yet clear if an elevated pulmonary pressure is a direct cause of death or a risk factor for multi-organ disease and generalized sickle cell vasculopathy, for patients with mild pulmonary hypertension (TRV 2.5 - 2.9 m/s) we recommend intensification of sickle cell-specific therapy. This would comprise:

- Hydroxyurea treatment at the maximum tolerated dose as defined by the Multicenter Study of Hydroxyurea, with erythropoietin therapy considered if reticulocytopenia limits hydroxyurea therapy.
- Monthly transfusion therapy may be considered for patients with a poor response to hydroxyurea, accompanied by chelation therapy, if indicated. Anecdotally, the TRV has declined in some patients with institution of these treatment measures, although to date this has not been prospectively studied.
- Consultation with a pulmonologist or cardiologist with experience in pulmonary hypertension, especially the latter if the echocardiogram shows evidence of left ventricular dysfunction.
- Identification and treatment of risk factors associated with pulmonary hypertension such as rest, exercise or nocturnal hypoxemia, sleep apnea, pulmonary thromboembolic disease, left ventricular systolic and diastolic dysfunction, severe anemia and iron-overload.

In addition to the above measures, practitioners treating patients with TRV \geq 3 m/s should consider:

- Right heart catheterization to assess left ventricular diastolic and systolic function.
- A CT-pulmonary angiogram to exclude chronic thromboembolic pulmonary hypertension.
- Consider systemic anticoagulation (shown by Rich et al. to improve outcomes in patients with primary pulmonary hypertension and in-situ thrombosis; note that no data are as yet available in patients with sickle cell disease).

In addition, practitioners treating these patients should also consider specific therapy with selective pulmonary vasodilator and remodeling drugs, particularly if the patient has symptomatic dyspnea on exertion which has progressed in recent months or years. Drugs which are FDA-approved for primary pulmonary hypertension include bosentan (Tracleer®) and various forms of prostaglandin therapy, none of which have been comprehensively investigated for sickle cell pulmonary hypertension. Derchi et al. and Machado et al. have considerable pilot experience with sildenafil, which has recently gained FDA approval for pulmonary hypertension under the trade name Revatio®. Two multicenter trials (sildenafil and bosentan) for hemolysis-associated pulmonary hypertension are anticipated in the near future.

Also, appropriate consultation and right heart catheterization is recommended at baseline and repeated annually.

More detailed management recommendations by Machado and Gladwin are available in a recently published review in the [*British Journal of Haematology*](#)

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Derchi G, Forni GL, Formisano F, et al. Efficacy and safety of sildenafil in the treatment of severe pulmonary hypertension in patients with hemoglobinopathies. *Haematologica*. 2005;90:452-8.
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Machado RF, Gladwin MT. Chronic sickle cell lung disease: new insights into the diagnosis, pathogenesis and treatment of pulmonary hypertension. *Br J Haematol*. 2005;129:449-64.
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Machado RF, Martyr S, Kato GJ, et al. Sildenafil therapy in patients with sickle cell disease and pulmonary hypertension. *Br J Haematol*. 2005;130:445-53.
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Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium channel blockers on survival in primary pulmonary hypertension. *N Engl J Med* 1992;327:76:81
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Other Vascular Complications of Hemolysis

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Nitric oxide regulates smooth muscle tone and platelet activation: its depletion can give rise to smooth muscle dystonia, causing clinical manifestations such as hypertension, gastrointestinal contraction, erectile dysfunction, and clot formation. Specific gastrointestinal symptoms can include abdominal pain, esophageal spasms, and dysphagia. As detailed by Rother and colleagues, these symptoms, common in the hemolytic crisis of paroxysmal nocturnal hemoglobinuria, also occurred in a dose-dependent fashion in normal volunteers who were infused with the early generation blood substitutes, which scavenged nitric oxide (and, consequently, prevented the clinical adoption of those agents). It is intriguing to speculate that these same symptoms, which occur in sickle cell disease, might be due not to sickling, but to depletion of nitric oxide due to intravascular hemolysis. We have proposed that the clinical manifestations of sickle cell disease may fall into two partially overlapping subphenotypes. The first subphenotype encompasses the more classic manifestations of the disease: vaso-occlusive crisis and the acute chest syndrome. These morbidities are epidemiologically associated with high white blood cell counts, high steady state hemoglobin levels and low fetal hemoglobin levels (increasing fetal hemoglobin concentration is protective). These complications are largely mediated by microvascular obstruction by sickle erythrocytes and their pathogenesis is characterized by ischemia-reperfusion injury, infarction and inflammation. The second subphenotype encompasses clinical complications shared by other hemolytic anemias, and includes pulmonary arterial hypertension, systemic systolic arterial hypertension, cutaneous leg ulceration, priapism, and possibly stroke.

While less clearly linked to hemolytic rate, there are a number of pathological and clinical features of stroke in patients with sickle cell disease that suggest a parallel pathobiology with the vasculopathy of pulmonary hypertension (G. Kato, et al., manuscript submitted). Stroke and pulmonary hypertension have many epidemiological risk factors in common, including history of prior stroke, systolic hypertension, low transcutaneous oxygen saturation, and severe anemia. Both show histopathological evidence of large vessel arterial disease, featuring smooth muscle hyperplasia with overlying endothelial damage, fibrosis, and thrombosis in situ. Fetal hemoglobin expression has not proven protective in either condition. The potential role of nitric oxide resistance in cerebrovascular disease remains to be investigated in sickle cell disease and thalassemia.

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2.

Kato GJ, Hsieh M, Machado R, Taylor VI J, Little J, Butman JA, Lehky T, Tisdale J, Gladwin MT. Cerebrovascular disease associated with sickle cell pulmonary hypertension. Manuscript submitted.

☰ Hemolysis and Priapism

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Priapism has been reported in patients with sickle cell disease, thalassemia intermedia, red cell enzymopathy, unstable hemoglobin disorders, and other hemolytic anemias. In the NIH pulmonary hypertension screening cohort, patients with a history of priapism had evidence of an increased hemolytic rate and were five-fold more likely to have pulmonary hypertension, supporting a mechanistic and epidemiological link between these complications. In a recent case-control analysis of data from the Comprehensive Study of Sickle Cell Disease (CSSCD) cohort study, Nolan et al found that priapism was associated with the laboratory markers of a high hemolytic rate and leukocytosis; a genetic polymorphism in *klotho*, a gene that regulates NO bioavailability, was also linked to priapism in the other Nolan study. Additionally, priapism was found to occur less frequently in patients with lower hemolytic rate such as hemoglobin SC disease and S-beta-plus-thalassemia. Additionally, the recent Champion et al study using mouse models suggests that priapism involves dysregulation of phosphodiesterase-5, the enzyme normally responsible for counterbalancing the nitric oxide effect, implicating the nitric oxide pathway rather than sickling. Evidence is mounting that priapism is a feature of intravascular hemolysis in general, and not only of sickling disorders.

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Nolan VG, Wyszynski DF, Farrer LA, Steinberg MH. Hemolysis-associated priapism in sickle cell disease. *Blood*. 2005 Jun 28; [Epub ahead of print]



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Nolan VG, Baldwin C, Ma Q, et al. Association of single nucleotide polymorphisms in *klotho* with priapism in sickle cell anaemia. *Br J Haematol*. 2005;128:266-272.



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Champion HC, Bivalacqua TJ, Takimoto E, et al. Phosphodiesterase-5A dysregulation in penile erectile tissue is a mechanism of priapism. *Proc Natl Acad Sci U S A*. 2005;102:1661-6.



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☰ Hemolysis and Leg Ulceration

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Cutaneous leg ulceration has also been associated with hemolytic anemias including sickle cell disease, thalassemia, and spherocytosis, the latter recently reported by Giraldi et al. Consistent with this shared complication of hemolytic anemias, in the CSSCD cohort, patients with a history of leg ulcers had the highest rates of hemolysis (personal communication; M. Steinberg). In the NIH pulmonary hypertension screening cohort described above, leg ulceration was associated with a history of priapism, pulmonary hypertension, and markers of more severe intravascular hemolysis. Leg ulceration is another complication of hemolytic disorders not limited to the sickling hemoglobinopathies. Due to the statistical association of leg ulceration, pulmonary hypertension and priapism, it is tempting to speculate that leg ulceration is also due in part to disruption in nitric oxide-dependent blood flow caused by chronic intravascular hemolysis. This, however, is an area that requires further research.

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☰ SOURCES FOR ADDITIONAL INFORMATION

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4. Vichinsky EP. [Pulmonary hypertension in sickle cell disease.](#) *N Engl J Med.* 2004;350:857-859.
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Learning Objectives

At the conclusion of this activity, participants should be able to:

- Describe the clinical significance of pulmonary hypertension in sickle cell disease and thalassemia
- Recognize a syndrome of pulmonary hypertension, priapism, leg ulcers, and possibly ischemic stroke in patients with hemoglobinopathies.
- Discuss the emerging pathophysiological linkage between intravascular hemolysis and vasculopathy due to associated endothelial dysfunction.

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