Pulmonary Hypertension Associated With Hemoglobinopathies
Prevalent But Overlooked

Dimitrios Farmakis, MD, PhD; Athanasios Aessopos, MD, PhD

Hemoglobinopathies constitute a heterogeneous group of hereditary hemoglobin disorders characterized by either reduced (thalassemias) or defective (sickle cell disease) globin chain synthesis that results in chronic hemolytic anemia. They represent the most common monogenetic disorders in humans, and although traditionally confined to specific geographic areas and populations (the Mediterranean Basin and the Middle and Far East in the case of specific geographic areas and populations (the Mediterranean disorders in humans, and although traditionally confined to anemia. They represent the most common monogenetic globin chain synthesis that results in chronic hemolytic reduced (thalassemias) or defective (sickle cell disease)

Epidemiology

β-Thalassemia

PH is a frequent finding in patients with hemoglobinopathies, but the reported prevalence varies in the different conditions and according to the method used for screening (Table 1). In thalassemia intermedia, a form of β-thalassemia that accounts for 20% to 25% of cases, PH has been recognized as the most striking cardiovascular finding and the main cause of heart failure. In a preliminary report, all 7 patients with thalassemia intermedia with heart failure had preserved systolic left ventricular (LV) function and severe PH as shown by right-sided heart catheterization. This initial report was followed by a systematic study of 110 patients with thalassemia intermedia with a mean age of 33 years; PH was observed echocardiographically in approximately 60% of cases, and all 6 patients with heart failure had preserved systolic LV function and underwent right-sided heart catheterization that confirmed the presence of PH. A later study comparing cardiovascular involvement between thalassemia intermedia and the most prevalent form of the disease, namely, thalassemia major, in a cohort of 205 patients confirmed the above findings. In thalassemia major, in contrast, the main cardiac manifestation is LV dysfunction.

Sickle Cell Disease

In homozygous sickle cell anemia, PH is a frequent finding and has been considered a major determinant of prognosis. In a cohort of 195 patients with a mean age of 36 years, 32% of patients had PH by echocardiography, and PH was the strongest predictor of mortality within 18 months. Similarly, in a subsequent trial in 235 patients with a mean age of 35 years, PH was present in 40% of cases, and together with diastolic LV dysfunction, it was the strongest predictor of mortality. In sickle-thalassemia, a compound heterozygous state with 1 thalassemia and 1 sickle allele, PH has been observed with a rather lower frequency and a definitely lesser severity. It should be stressed that with the exception of thalassemia intermedia, in which PH was confirmed by right-sided heart catheterization in 2 of the previously cited trials, the vast majority of studies in thalassemia and sickle cell disease used echocardiography as a screening tool, and therefore, the reported prevalence may be overestimated by at least some of those trials.

Pathophysiology

The hemoglobinopathies are not the only hemolytic states associated with PH. In fact, this association is much broader, and it has been observed that other chronic hemolytic...
conditions, such as hereditary spherocytosis, microangiopathic hemolytic anemia, and paroxysmal nocturnal hemoglobinuria, also have an increased occurrence of PH.\textsuperscript{19,20} Hemolysis is believed to play a key role in the development of PH in these patients. It has been shown that chronic hemolysis leads to nitric oxide depletion due to nitric oxide scavenging, arginine catabolism, and endogenous nitric oxide synthesis inhibition, as well as to enhanced platelet activation and increased endothelin-1 release.\textsuperscript{18,21} All of those events in turn lead to a vasculopathy\textsuperscript{18,22} characterized by endothelial dysfunction, increased vascular tone, inflammation, and hypercoagulability, and finally, to vascular remodeling and destruction of pulmonary vasculature, which ultimately results in hemolytic anemia–associated PH.

Recently, some authors have questioned the contribution of the above pathogenetic link and have argued against the severity and prognostic significance of PH in sickle cell disease.\textsuperscript{24} In fact, it has been shown that 85% of patients >30 years of age who have thalassemia intermedia have at least 1 of the typical manifestations of the defect, namely, skin lesions, ocular angioid streaks, and arterial degeneration,\textsuperscript{25} whereas subclinical pathology findings were found in 96% of young patients with thalassemia major and other hemolytic conditions.\textsuperscript{26} This defect has been related to a number of vascular and other complications,\textsuperscript{27,28} including pulmonary arterial lesions, hence providing a structural component to the aforementioned hemolysis-related vasculopathy.\textsuperscript{22}

A hypercoagulable state is another notable finding in hemoglobinopathies.\textsuperscript{29} Hypercoagulability results from a spectrum of abnormalities, including the native erythrocyte precoagulant surface, the frequently performed splenectomy, some coexistent genetic coagulation defects, and the previously mentioned endothelial dysfunction and vasculopathy.\textsuperscript{30} More recent clinical and experimental studies suggest an interaction between hemolysis, platelet or coagulation activation, and decreased nitric oxide bioavailability both in sickle cell disease\textsuperscript{31,32} and in other hemolytic conditions such as paroxysmal nocturnal hemoglobinuria.\textsuperscript{26} Several thromboembolic complications have been reported in hemoglobinopathy patients, especially in those with thalassemia intermedia and splenectomy or sickle cell disease, including pulmonary embolism and in situ thrombosis.\textsuperscript{30,33} Besides hemolysis-related vasculopathy and hypercoagulability, further lung injury in patients with hemoglobinopathies results from additional disorders, such as vaso-occlusive crises and acute chest syndrome in sickle cell disease, iron overload in transfusion-dependent cases, recurrent respiratory tract infections, and the aforementioned elastic tissue defect.\textsuperscript{18,30}

### Table 1. Prevalence of Pulmonary Hypertension in Different Hemoglobinopathies

<table>
<thead>
<tr>
<th>Study</th>
<th>Publication Year</th>
<th>Hemoglobinopathy</th>
<th>Method for PH Diagnosis</th>
<th>Echocardiographic Criterion for PH</th>
<th>Prevalence of PH, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerasou et al\textsuperscript{3}</td>
<td>1990</td>
<td>Thalassemia major</td>
<td>Echo</td>
<td>PAT/RVET</td>
<td>75</td>
</tr>
<tr>
<td>Du et al\textsuperscript{4}</td>
<td>1997</td>
<td>Thalassemia major</td>
<td>Echo</td>
<td>TPG + RAP &gt;30 mm Hg</td>
<td>79</td>
</tr>
<tr>
<td>Derchi et al\textsuperscript{5}</td>
<td>1999</td>
<td>Thalassemia major</td>
<td>Echo</td>
<td>TPG</td>
<td>10</td>
</tr>
<tr>
<td>Aessopos et al\textsuperscript{6}</td>
<td>2004</td>
<td>Thalassemia major</td>
<td>Echo</td>
<td>TPG &gt;30 mm Hg</td>
<td>10</td>
</tr>
<tr>
<td>Aessopos et al\textsuperscript{7}</td>
<td>2005</td>
<td>Thalassemia major and thalassemia intermedia</td>
<td>Echo</td>
<td>TPG &gt;30 mm Hg</td>
<td>10</td>
</tr>
<tr>
<td>Aessopos et al\textsuperscript{8}</td>
<td>1995</td>
<td>Thalassemia intermedia with heart failure</td>
<td>RHC</td>
<td>RHC</td>
<td>100</td>
</tr>
<tr>
<td>Aessopos et al\textsuperscript{9}</td>
<td>2001</td>
<td>Thalassemia intermedia</td>
<td>Echo and RHC</td>
<td>TPG &gt;30 mm Hg</td>
<td>59</td>
</tr>
<tr>
<td>Gladwin et al\textsuperscript{10}</td>
<td>2004</td>
<td>Sickle cell anemia</td>
<td>Echo</td>
<td>TRV ≥2.5 m/s</td>
<td>32</td>
</tr>
<tr>
<td>Machado et al\textsuperscript{11}</td>
<td>2006</td>
<td>Sickle cell anemia</td>
<td>Echo</td>
<td>TRV ≥2.5 m/s</td>
<td>35</td>
</tr>
<tr>
<td>Sachdev et al\textsuperscript{12}</td>
<td>2007</td>
<td>Sickle cell anemia</td>
<td>Echo</td>
<td>TRV ≥2.5 m/s</td>
<td>40</td>
</tr>
<tr>
<td>De Castro et al\textsuperscript{13}</td>
<td>2008</td>
<td>Sickle cell anemia, sickle thalassemia, sickle HbC, sickle Hb0Arab</td>
<td>Echo</td>
<td>TRV ≥2.5 m/s</td>
<td>32</td>
</tr>
<tr>
<td>Klings et al\textsuperscript{14}</td>
<td>2008</td>
<td>Sickle cell anemia</td>
<td>Echo</td>
<td>TRV ≥2.5 m/s</td>
<td>43</td>
</tr>
<tr>
<td>Moysakis et al\textsuperscript{15}</td>
<td>2005</td>
<td>Sickle thalassemia</td>
<td>Echo</td>
<td>TPG &gt;30 mm Hg</td>
<td>21</td>
</tr>
<tr>
<td>Voskaridou et al\textsuperscript{16}</td>
<td>2007</td>
<td>Sickle thalassemia</td>
<td>Echo</td>
<td>TPG + RAP ≥35 mm Hg or TRV ≥2.5 m/s</td>
<td>33</td>
</tr>
<tr>
<td>Aessopos et al\textsuperscript{17}</td>
<td>2009</td>
<td>Sickle thalassemia</td>
<td>Echo</td>
<td>TPG &gt;30 mm Hg</td>
<td>27</td>
</tr>
</tbody>
</table>

PH indicates pulmonary hypertension; Echo, echocardiography; PAT/RVET, pulmonary valve acceleration time to right ventricular ejection time ratio; TPG, tricuspid systolic pressure gradient; RAP, right atrial pressure; RHC, right heart catheterization; sickle-HbC, sickle cell–hemoglobin C; sickle-HbOArab, sickle cell–hemoglobin O-Arab; and TRV, tricuspid regurgitation velocity.
In addition to pulmonary arterial disorders, lung disease, and thromboembolic events, patients with hemoglobinopathies have an increased occurrence of left-sided heart disease, and it is well known that up to 60% of cases with severe systolic LV dysfunction and up to 70% of those with isolated diastolic LV dysfunction develop some degree of PH. LV dilatation and eccentric hypertrophy are common in all hemoglobinopathy patients. Interestingly, even in a cohort of optimally treated thalassemia major patients, 7% of cases had impaired systolic function and 38% had restrictive LV filling. Left-sided valvular disease has also been encountered at a higher percentage than in normal individuals of similar ages, especially in the form of mitral regurgitation and prolapse. The main mechanisms involved in the pathogenesis of left-sided heart disease in hemoglobinopathies include high-output state, iron overload, myocarditis, and other immunogenic factors, as well as the aforementioned elastic tissue defect.

Chronic anemia induces a compensatory high-output state and volume overload. This is particularly evident in hemoglobinopathies, in which high cardiac output is related to the chronic tissue hypoxia that results from low total hemoglobin levels and increased levels of hemoglobin F, compensatory bone marrow expansion, splenomegaly, and coexistent hepatic injury. It has been shown that even optimally transfused patients with thalassemia major have increased levels of cardiac output. A high-output state damages the pulmonary vasculature and hence contributes to the pathogenesis of PH, while at the same time, it may lead to overestimation of pulmonary artery pressure for a given level of pulmonary vascular resistance, particularly when the assessment relies only on echocardiography. Finally, hepatic injury, resulting from iron overload, blood-borne viral infections, and bone marrow expansion, may lead to cirrhosis and thus development of portopulmonary hypertension.

The combined effects of the aforementioned factors increase pulmonary resistance and cardiac output and thus lead to the development of PH (Figure). Hence, it is clear that hemolytic anemia–associated PH is a complex condition with multiple pathogenetic mechanisms that encompass essentially all categories of PH. In several cases, a multifactorial vasculopathy related to chronic hemolysis may lead to pulmonary arterial hypertension, and therefore, chronic hemolytic states, including the hemoglobinopathies, have been classified lately as conditions that potentially are associated with pulmonary hypertension.
Table 2. Studies of Phosphodiesterase-5 Inhibitors and Endothelin Receptor Antagonists in Patients With Hemoglobinopathies

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Hemoglobinopathy</th>
<th>N</th>
<th>Duration</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derchi et al</td>
<td>Sildenafil</td>
<td>Thalassemia intermedia, thalassemia major, sickle thalassemia</td>
<td>7</td>
<td>12–48 mo</td>
<td>↓ TRV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ NYHA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ 6MWT</td>
</tr>
<tr>
<td>Machado et al</td>
<td>Sildenafil</td>
<td>Sickle cell anemia</td>
<td>12</td>
<td>6 mo</td>
<td>↓ TRV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ mPAP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ 6MWT</td>
</tr>
<tr>
<td>Little et al</td>
<td>Sildenafil vs L-arginine*</td>
<td>Sickle cell anemia</td>
<td>14</td>
<td></td>
<td>↓ TRV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ 6MWT</td>
</tr>
<tr>
<td>Minniti et al</td>
<td>Bosentan or ambrisentan</td>
<td>Sickle cell anemia</td>
<td>8</td>
<td>≥6 mo</td>
<td>↓ TRV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ mPAP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ 6MWT</td>
</tr>
<tr>
<td>Barst et al</td>
<td>Bosentan vs placebo</td>
<td>Sickle cell anemia</td>
<td>26</td>
<td>4 mo</td>
<td>↓ PVR (NS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ CO (NS)</td>
</tr>
</tbody>
</table>

TRV indicates tricuspid regurgitant jet velocity; NYHA, New York Heart Association class; 6MWT, 6-minute walk test; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; CO, cardiac output; and NS, nonsignificant.
*In addition to hydroxyurea.

arterial hypertension (group 1). Right-sided heart catheterization in 26 patients with sickle cell anemia and PH revealed that 54% had pulmonary arterial hypertension, whereas the remainder (46%) had pulmonary venous hypertension. Furthermore, PH may result from the frequently coexistent left-sided heart disease (group 2) or pulmonary disease (group 3), from pulmonary thromboembolism in the context of a hypercoagulable state (group 4), or from the presence of a high-output state and volume overload, or it may be of multifactorial or unknown origin (group 5).

Therapeutic Considerations

The complexity of the disorder is not the only reason why the issue of PH in hemoglobinopathies should be addressed. A second reason is that, although the hemoglobinopathies have a worldwide distribution, and there is a high prevalence of PH among these patients, this problem is often overlooked, and usually is unknown to the general cardiovascular physician. Finally, and most importantly, there are several hemoglobinopathy-specific, effective measures that can be used for the prevention of PH, as well as for its treatment.

Screening for PH should be an essential component of the hemoglobinopathy patient’s assessment and may be accomplished by transthoracic Doppler echocardiography. Doppler echocardiography is the most established screening tool for PH in general, is widely available, is cost-effective, and is part of the normal cardiovascular examination of hemoglobinopathy patients. However, echocardiography may overestimate pulmonary artery pressure, thus providing false-positive results, and therefore, any positive findings should be confirmed by right-sided heart catheterization.

Anticoagulation and novel drug categories, including phosphodiesterase-5 inhibitors, endothelin receptor antagonists, and prostacyclin analogues, have been introduced for the management of pulmonary arterial hypertension. Some novel agents have also been tested in patients with hemoglobinopathies. A few small clinical trials with phosphodiesterase-5 inhibitors and endothelin antagonists have been published (Table 2), but there is still no randomized, controlled trial demonstrating a benefit of any of the currently available pulmonary arterial hypertension–specific medications in patients with hemoglobinopathies. A randomized trial of sildenafil in patients with sickle cell disease sponsored by the National Institutes of Health was halted before completion because of the increased occurrence of painful crises in the sildenafil arm and the lack of benefit from this agent. Furthermore, the ASSET trials of bosentan in sickle cell disease (Assessment in Patients with Sickle Cell Disease of the Efficacy and Safety of Bosentan Therapy on Pulmonary Arterial Hypertension) were also suspended early because of poor enrollment, and some of the beneficial effects observed were not statistically significant. Until further studies clarify the effectiveness and safety of novel agents in hemoglobinopathies, the management of those patients should focus on the disease-specific therapeutic targets that derive from the diverse pathogenetic mechanisms involved.

Proper transfusion therapy restores tissue oxygen delivery and suppresses the synthesis of native defective erythrocytes, hence preventing hemolysis, hypercoagulability, tissue hypoxia, and volume overload, and therefore may theoretically have an important role in the prevention and treatment of PH in those patients. Along with blood transfusions, concomitant iron chelation therapy prevents iron accumulation and the resulting oxidative tissue damage, including ventricular dysfunction and lung injury. Furthermore, hydroxyurea modifies the defective hemoglobin synthesis and reduces thrombocytosis, hence preventing hemolysis and hypercoagulability. In a recent study of 584 patients with thalassemia intermedia, those 3 hematologic therapeutic modalities proved to be protective against PH; however, the trial was retrospective and nonrandomized, and pulmonary artery pressure was evaluated only by echocardiography. Other smaller studies or case reports in patients with thalassemia have also provided some preliminary evidence that blood transfusions or hydroxyurea therapy may have some beneficial effects on PH. Prospective randomized trials or other forms of hard
evidence on this issue are still missing and may be an important field for future research.

In summary, PH in patients with hemoglobinopathies, although frequently overlooked, represents a prevalent clinical entity with significant prognostic implications and a complex pathophysiology that requires a particular management with disease-specific measures that may prevent its development.

Disclosures
None.

References


**Key Words:** hypertension, pulmonary hypertension, hemoglobinopathies, beta-thalassemia, sickle cell disease
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