Sickle Cell Pulmonary Hypertension: Pathogenesis and Diagnosis

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Received 29 July, 2017 Published 20 Aug, 2017

Abstract

Pulmonary hypertension (PHT) is a common symptom associated with patients suffering from sickle cell disease (SCD). The patients show mild elevation in pulmonary artery pressure along with high morbidity and mortality rate. PHT etiology is multifactorial that includes hemolysis, chronic liver disease, vascular injury resulting due to sequestration of sickle red blood cells (RBCs) and asplenia. The aim of this mini-review is to summarize the pathogenesis and diagnosis of PHT in SCD patients.

Keywords: Pulmonary Hypertension; Hemolysis; Sickle Cell Disease; Exertional Hypertension.

Background

Sickle cell disease (SCD) refers to the inherited disorder of red blood cells (RBCs). The disorder is marked by point mutation occurring in the beta (β)-globin chain of hemoglobin. This results in the amino acid substitution of valine in place of glutamic acid at position 6 (Glu6Val) of the chain, leading to the formation of abnormal sickle hemoglobin (HbS) [1]. On exposure to low-oxygen tension, HbS loses its solubility capacity, resulting in polymerization and aggregation of mutated hemoglobin inside sickle RBCs as they traverse in microcirculation [2]. The sickled RBCs obstruct blood vessels and impede free blood flow in the affected vessel causing oxygen deprivation, vascular congestion, lactate acidosis, anaerobic glycolysis, and pain [3]. In general, SCD manifestations are secondary to ischemia from vessel occlusion and hemolysis from rupture of sickle cells with less deformable RBCs [4]. However, the severity of complications varies between patients.

In adult SCD patients, pulmonary complications accounted for a large number of deaths [5-8]. Furthermore, Steinberg et al. [9] reported that in 28% of all deaths in SCD, pulmonary complications were found to be the most common cause.

In SCD, both acute and chronic pulmonary complications are common but frequently under-appreciated by health care providers. Asthma and acute chest syndrome (ACS) are considered to be acute pulmonary complications, whereas pulmonary fibrosis, pulmonary hypertension (PHT) and cor pulmonale are considered as chronic pulmonary complications [10,11]. Among these chronic cardiopulmonary complications associated with SCD, PHT has appeared to be the most notable threat towards the safety and longevity of patients with SCD [12].

Pulmonary Hypertension

PHT is a life-threatening complication associated with SCD [13]. Reports have shown approximately 30% prevalence of PHT in these SCD patients [14-17]. The disease is an inherited and chronic blood disorder that includes SCD, thalassemia, hereditary spherocytosis and paroxysmal nocturnal hemoglobinuria (PNH) [13,15]. Although the etiology of SCD-related pulmonary hypertension is unclear, many retrospective studies have shown that SCD patients with PHT have an increased mortality rate compared to those without PHT [13, 15, 18].

The disease is characterized by an elevated pulmonary vascular resistance and pulmonary artery pressure (PAP) [12]. Recently, autopsy studies showed that nearly 95% of SCD patients exhibited histological evidence of pulmonary arterial hypertension at the time of death [19]. Moreover, a previous study has showed that SCD patients with PHT have a significantly higher mortality rate compared to patients without PHT [12].

Clinical Presentation

Diagnosing the prevalence of PHT in SCD patients can be challenging. PHT is associated with common symptoms like exertional hypertension (most frequently observed), which is also a symptom associated with chronic anemia. Hence, a high index of doubt for
the disease is necessary for its diagnosis and detection. Patients with severe PHT present with more specific symptoms including lower extremity edema, syncope, and angina.

It is essential to highlight that PHT in SCD patients is a unique disorder compared to other types of pulmonary arterial hypertension, given the existence of chronic anemia, which involves a resting high cardiac output to make up for a low oxygen carrying capacity [12]. Furthermore, it is possible that in patients suffering from significant anemia, any level of PHT could be weakly tolerated that might result in significant morbidity and probable mortality [12].

**Pathogenesis**

The hemoglobinopathies are not the only hemolytic states linked with PHT. In general, it has been noticed that other chronic hemolytic disorders, for instance hereditary spherocytosis, paroxysmal nocturnal hemoglobinuria (PNH), and microangiopathic hemolytic anemia, also have an increased occurrence of PHT [20, 21].

Hemolysis is thought to play a major role in the development of PHT. It has been reported that chronic hemolysis results in nitric oxide (NO) reduction due to NO scavenging, endogenous NO synthesis inhibition, and arginine catabolism, in addition to increased endothelin-1 release and enhance platelet activation [22, 23]. These events consecutively cause vasculopathy [22, 24] characterized by increased vascular tone, endothelial dysfunction, hypercoagulability, and inflammation. Furthermore, vascular remodeling and destruction of pulmonary vasculature eventually resulted in hemolytic anemia (HA)-associated PHT [25] (Figure 1).

**Figure 1:** Flowchart representing pathogenesis of PHT

**Hemolysis**

The key factor in the development of PHT is chronic intravascular hemolysis [23, 26, 27]. Hb is released into blood plasma and reacts with NO and later destroys it as an outcome of hemolysis. This results in abnormally elevated rates of NO utilization and leads to a state of NO resistance. In addition, NO plays a crucial role in maintaining vasodilatation and also inhibits platelet aggregation and attachment, down-regulate adhesion molecules, and limits ischemia-perfusion injury [17]. RBC breakdown, during hemolysis, releases hemoglobin (Hb), and the enzyme arginase into the circulation. Cell-free hemoglobin has been shown to be a powerful scavenger of NO, efficiently preventing these vasoprotective properties [26]. Furthermore, arginase depletes the substrate for NO synthesis by switching of arginine to ornithine, compounding the state of reduced NO bioavailability.

Intravascular hemolysis presents the possibility towards a procoagulant state. NO severely inhibits platelet activation that may consecutively be blocked by Hb-mediated NO scavenging [12]. In addition, HA is associated with Hb desaturation and ventilation/perfusion in homogeneity [28,29]. These mediators might create a proliferative vasculopathy in the lung and other organs, as in the kidney.

**Thrombosis**

Low levels of proteins C and S, increased activation of tissue factors, and elevated levels of thrombin-antithrombin complexes and D-dimers, also known as a hypercoagulable state, are seen in SCD patients in steady-state [12]. This state could promote vascular obstruction. Autopsy studies showed that in situ thrombosis is observed in both SCD patients and idiopathic pulmonary arterial hypertension [30-32]. Recently, autopsy studies suggest that thrombosis mostly occurs in situ, which is similar to what occurs in other forms of pulmonary arterial hypertension [19].

**Hypoxia**

Broncho-reactive lung disease, such as chronic lung injury, undetected episodes of regional pulmonary hypoxia, and fat metabolism may result in a vicious cycle of chronic fibrotic pulmonary parenchymal damage, vascular proliferation, hypoxia, altered vascular tone, and a consequent pulmonary vasculopathy [12]. Gladwin et al. [27] reported that the number of episodes of acute chest syndrome was not associated with PHT. Furthermore, restrictive ventilatory defects and pulmonary fibrosis have also been reported in thalassemia patients [33,34]. These data suggest similar pathologic mechanisms that lead to PHT, which could also be involved in the genesis of pulmonary fibrosis in SCD patients.

**Asplenia**

Functional asplenia may lead to the development of PHT in SCD patients. Splenectomy has been shown to be a risk factor for PHT development, mainly in patients with hemolytic postsplenectomy disorders [12, 35]. It has been hypothesized that the loss of splenic performance amplifies the circulation of platelet-derived mediators
and that in the circulation, senescent and abnormal RBCs trigger platelet activation, promoting pulmonary microthrombosis and RBC adhesion to the endothelium [12].

**Diagnostic Evaluation**

Assessment of SCD patients suspected with PHT should follow the guiding principle that is recognized for other causes of PHT. Two stages of analysis that are frequently involved are (1) detection of PHT while evaluating a symptomatic patient or during generalized screening tests and (2) cardiopulmonary characterization involving diagnostic tests that characterize other associated diseases, such as hemodynamic perturbations (along with their etiology) and degree of functional impairment [12].

**Assessment of Functionality**

The World Health Organization classification needs to be followed for quantification of the level of symptomatic exercise constraint that will be used in assessing treatment response (Table 1) [12]. The 6-minutes walk test is the most frequently utilized work out test in PHT patients. Although this test has not been confirmed in SCD patients, Machado et al. [17] have reported the 6-min walk test to be directly related to peak oxygen consumption and inversely related to the PHT level. Hence, the study signifies the benefit of using 6-min walk distance test enhanced with therapy in SCD patients.

**Table 1:** World Health Organization of Functional status of patients with PHT [17].

<table>
<thead>
<tr>
<th>Classes</th>
<th>World Health Organization Classification of Functional Status of Patients with Pulmonary Hypertension</th>
</tr>
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<tbody>
<tr>
<td>Class I</td>
<td>Patients with PHT but without resulting limitation of physical activity.</td>
</tr>
<tr>
<td>Class II</td>
<td>Patients with PHT resulting in slight limitation of physical activity.</td>
</tr>
<tr>
<td>Class III</td>
<td>Patients with PHT resulting in marked limitation of physical activity.</td>
</tr>
<tr>
<td>Class IV</td>
<td>Patients with PHT resulting in the inability to carry out any physical activity without symptoms</td>
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</table>

*Note: Adapted from Gray A, Animonwu E, Davies S, et al. (1991).*

**Laboratory Analysis**

Serological analysis is essential for screening liver function, collagen vascular disorders, and HIV testing. Furthermore, the degree and severity of hemolytic anemia and iron overload should also be analyzed.

**Transthoracic Doppler Echocardiography**

This test provides information on non-invasive estimation of pulmonary artery systolic pressure, right and left ventricular function, and valvular function. Using echocardiography in SCD patients, estimation of pulmonary artery systolic pressure has been validated [27].

**Ventilation-Perfusion Lung Scintigraphy (V/Q)**

Chronic thromboembolic pulmonary embolism is a curable symptom of PHT. Hence, its assessment is considered important, which is done by this recommended method. V/Q scans shows that the patients with the mentioned symptoms have no less than one large perfusion defect, which is significant in SCD patients in which thromboembolism seems as a reason of mortality [12].

**Radiographic Studies**

Chest X-ray is a low sensitivity test for diagnosing PHT. However, right ventricular enlargement or central pulmonary arterial can confirm the presence of the disease. Furthermore, pulmonary fibrosis could also be seen in chest X-ray. High-resolution computerized tomography (CT) of the chest reveals a detailed view of the pulmonary parenchyma and might lead to the identification of pulmonary fibrosis, which is seen in SCD patients [12].

**Overnight Oximetry**

The development of PHT can result due to severe sleep apnea syndrome, which causes frequent episodes of night-time desaturation. The overnight oximetry test can confirm the presence of PHT. Furthermore, night-time oxygen desaturation is a well documented entity in SCD patients [36-38].

**Pulmonary Function Test**

Pulmonary function testing will rule out or recognize the presence of pulmonary parenchymal disease or airflow obstruction that might potentially aggravate PHT associated with hypoxemia. Most SCD patients develop abnormal pulmonary function characterized by restrictive lung disease, airflow obstruction, hypoxemia, and abnormal diffusing capacity [39-41].

**Right Heart Catheterization (RHC)**

RHC is a critical test for verifying the diagnosis of PHT and assessing its severity, at the same time excluding other contributors, for instance major left ventricular dysfunction [12]. The test remains the gold standard for diagnosing PHT [42].

**Conclusion**

PHT is a frequent complication seen in patients with SCD, which is associated with high morbidity and mortality rate. Based on this, echocardiographic screening for the existence of pulmonary hypertension should be strongly considered as a method of diagnosis in adult SCD patients. Given the possible association between hemolysis and pulmonary hypertension, it is possible that intensification of SCD-specific treatment can limit the development of the disease at its earliest stages and at later stages and could potentially reduce the associated morbidity and mortality. In the end, large randomized trials need to be carried out to fully understand the biology of PHT in the case of SCD patients and other hemolytic disorders.
Acknowledgment

The author is thankful to www.manuscriptedit.com for providing English language editing and proofreading services for this manuscript.

References

355(9214): 1476-1478.


