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Review article

Pulmonary hypertension in chronic hemolytic anemias: Pathophysiology and treatment

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ABSTRACT

Pulmonary hypertension has emerged as a major cause of morbidity and mortality in patients with hemoglobinopathies and chronic hemolytic anemias. These hematological diseases include – but are not limited to – sickle cell disease (SCD), thalassemia, paroxysmal nocturnal hematuria, and hereditary spherocytosis. Although most studies have been based on the use of echocardiography as a screening tool for pulmonary hypertension as opposed to the gold standard of right heart catheterization for definitive diagnosis, the association between chronic hemolytic anemia and pulmonary hypertension is evident. Studies have shown that patients with SCD and a tricuspid regurgitant velocity (TRV) ≥ 2.5 m/sec are at increased risk of pulmonary hypertension and are at increased mortality risk. Additional markers of risk of pulmonary hypertension and increased mortality include a pro-BNP > 160 pg/mL combined with a 6-min walk distance of < 333 m. There is currently a lack of concrete data to support the use of targeted oral pulmonary arterial hypertension therapy in chronic hemolytic anemia. As a result, management is generally targeted towards medical optimization of the underlying anemia. This literature review aims to discuss the pathophysiology, diagnostic and prognostic tools, recent studies and current protocols that are essential in guiding management of pulmonary hypertension in chronic hemolytic anemias.

1. Introduction

Pulmonary hypertension is defined by a mean pulmonary artery pressure sustained above 25 mmHg at rest [1]. There are five categories of pulmonary hypertension in the current classification, as shown in Table 1 [2]. Pulmonary hypertension associated with chronic hemolytic anemia had been previously classified within the Group 1 category (pulmonary arterial hypertension), but was re-categorized into Group 5, conditions of unclear or multifactorial origin, at the Fifth World Symposium on Pulmonary Hypertension in 2013 [2]. Depending on hemodynamics, pulmonary hypertension can also be characterized as pre-capillary or post-capillary patterns measured at right heart catheterization. Pre-capillary pulmonary hypertension is defined as when the pulmonary capillary wedge pressure is ≤ 15 mmHg, whereas post-capillary pulmonary hypertension is when the PAWP (or LVEDP) is > 15 mmHg [3]. A distinction between pre-capillary and post-capillary hypertension is often key to guiding management.

2. Pathophysiology

As indicated in their current classification within Group 5, there are multiple possible mechanisms that underlie the pathogenesis of pulmonary hypertension in hematological diseases. Pulmonary hypertension caused by hematological diseases can be associated with pre-capillary etiologies, post-capillary etiologies, or a combination. The mechanisms may be associated with hemolysis and its consequences, chronic anemia leading to high cardiac output, or with a hypercoagulable state. Nitric oxide normally plays a key role as a potent vasodilator and modulator of endothelial proliferation, along with having anti-inflammatory properties [4]. Depletion of nitric oxide and its precursor, Arginine, has been shown to correlate with a higher incidence of pulmonary hypertension. Intravascular hemolysis releases free hemoglobin and arginase-1, which both cause decreased nitric oxide signaling via different pathways. Free hemoglobin directly inactivates nitric oxide, while arginase-1 depletes a substrate of NO synthase, L-arginine. Both pathways lead to a decrease in nitric oxide and impair vascular endothelial function, which may result in pre-capillary pulmonary hypertension [4,5]. Hemolysis also enhances reactive

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Table 1
Classification of pulmonary hypertension.
Adapted from: Galiè N, Corris PA, Frost A, Girgis RE, Granton J, Jing ZC, et al. Updated Treatment Algorithm of Pulmonary Arterial Hypertension. Journal of the American College of Cardiology. 2013; 62 (25, Supplement):D60-D72. This classification may change somewhat following the 6th World Symposium of Pulmonary Hypertension, Nice France, February 2018

Group	Description
1	Pulmonary arterial hypertension: • Idiopathic PAH • Heritable PAH • Drug and toxin-induced • Associated conditions: connective tissue disease, HIV, portal hypertension, congenital heart diseases, schistosomiasis
2	Pulmonary hypertension secondary to left heart disease
3	Pulmonary hypertension secondary to lung diseases and/or hypoxia
4	Chronic thromboembolic pulmonary hypertension • Embolic disease • *In situ* thrombosis
5	Pulmonary hypertension with unclear or multifactorial mechanisms • Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy • Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis • Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders • Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

oxygen species and the oxidation of hemoglobin has been shown to activate Toll-Like Receptor 4, promote vaso-occlusion and acute lung injury, particularly in SCD. The activation of these sterile-inflammatory molecules via the heme-TLR4 pathway have been termed damage-associated molecular pattern molecules (DAMPs) [6]. Aside from hemolysis, chronic anemia may also cause a high cardiac output state that leads to left-sided heart disease, left ventricular dysfunction, and predisposes patients to post-capillary pulmonary hypertension. Hemolysis also causes oxidative damage to tissues, activating platelets and the coagulation cascade, resulting in vasculopathy and hypercoagulability [7]. As a result, patients are at an increased risk of developing deep venous thrombosis and pulmonary embolism, which may lead to one of the major categories of pulmonary hypertension (Group 4). It should be noted that patients with Group 1 PAH have also been shown to have increased hypercoagulability due to thrombotic arteriopathy, abnormalities of serum coagulation factors, anti-thrombotic factors, and fibrinolytic system that leads to a pro-thrombotic state. Furthermore, patients with SCD are prone to develop *in situ thrombosis* at the level of the small pulmonary vessels from recurrent vaso-occlusive crisis, which could also result in pulmonary hypertension [8].

Histopathologically in pulmonary arterial hypertension, all three layers of the pulmonary arterial wall – the intima, adventitia, media, and adventia – are affected via medial hypertrophy, migration of smooth muscle cells from the media to endothelial cells, and intimal proliferation [9]. The adventitia itself is thickened due to the expansion of cells in the media due to the accumulation of immune cells, such as fibroblasts and macrophages [10]. All groups of pulmonary hypertension may exhibit these histopathological findings, with Group 2 disease also showing prominently enlarged pulmonary veins and capillaries and Group 4 disease having organized thrombi replacing the intima of the proximal or distal elastic pulmonary arteries and attach to the medial layer [11]. As pulmonary hypertension in chronic hemolytic diseases is secondary to hemolysis, hypoxia, hypercoagulability or a combination of these factors, they may show any of the histopathological features described above.

The treatment of some hematological disorders themselves could also predispose patients to the development of pulmonary hypertension. Patients with hemoglobinopathies, such as SCD and β-thalassemia, are occasionally managed with blood transfusions. This may lead to iron-overload, especially in transfusion-dependent patients, which may induce myocardial iron deposition and/or interstitial pulmonary fibrosis and, ultimately, affect the left ventricular systolic or diastolic function and pulmonary vascular resistance [12]. Splenectomy, whether via surgery or auto-infarction, is also a risk factor for pulmonary hypertension, particularly chronic thromboembolic pulmonary hypertension (CTEPH). This is postulated to be due to an increased susceptibility to thrombosis resulting from high platelet counts and platelet aggregation or an increased amount of damaged red blood cells and adhesion to endothelium after splenectomy. The spleen is also responsible for clearing circulating microparticles, which are involved with inflammatory modulation, cytokine secretion, and expression of adhesion molecules [13]. Splenectomy causes decreased clearance of microparticles, resulting in inflammation and vascular remodeling that has been hypothesized to result in pulmonary hypertension [14]. Circulating microparticles of platelet and erythrocyte origins have been shown to impair endothelial vaso-relaxation by decreasing nitric oxide production during times of oxidative stress, thereby, altering pulmonary vascular tone and predisposing to the development of pulmonary hypertension [13]. These effects of splenectomy, coupled with the intrinsic complications of hemolytic disorders as described above, further predispose patients to pulmonary hypertension [12,15].

3. Diagnosis, screening & prognosis

The clinical presentation of pulmonary hypertension is often non-specific, mainly manifesting as dyspnea (particularly on exertion), fatigue, and, in more advanced disease, signs and symptoms of heart failure [16]. As a result, a high clinical suspicion is required for diagnosis, especially in at-risk patient populations. Right heart catheterization remains the gold standard diagnostic tool for pulmonary hypertension, with a mean pulmonary artery pressure ≥ 25 mmHg meeting the definition criterion. A subclass of pulmonary hypertension, pulmonary arterial hypertension (PAH), has an additional criteria of a pulmonary capillary wedge pressure ≤ 15 mm Hg [17]. An elevated pulmonary vascular resistance of > 3 Wood units is another criterion for pulmonary arterial hypertension [18]. Patients with chronic anemia have a reduced blood viscosity, which with an increased cardiac output, result in a lower pulmonary vascular resistance (PVR) compared with non-anemic patients. This is because measurement of PVR is inversely proportional to cardiac output. As a result, patients with increased cardiac output would have a lower PVR at baseline. Due to this physiology, patients with high cardiac output secondary to anemia should have an alternate definition of pulmonary hypertension. For sickle cell patients, the American Thoracic Society's Ad Hoc Committee on Pulmonary Hypertension of SCD has suggested > 2 Wood units to be diagnostic of elevated pulmonary vascular resistance [19]. However, few guidelines are available for other types of hemolytic anemias and whether this revised definition can be generalized to include other hemoglobinopathies remain in question.

Echocardiography is the main screening tool for pulmonary hypertension by measuring the tricuspid regurgitation velocity (TRV), with a TRV ≥ 3.0 m/sec beginning to suggest increased pulmonary arterial pressures in the general population. The TRV threshold for the SCD population to suggest increased pulmonary arterial pressures, on the other hand, is lower at TRV ≥ 2.5 m/sec as SCD patients have been shown to have increased mortality at this threshold [19]. However, echocardiographic findings are not diagnostic for pulmonary hypertension because hemodynamic effects could cause discrepancies in result interpretations. For instance, patients with hemoglobinopathies are prone to developing a hyperdynamic circulation because of an increased cardiac output secondary to chronic anemia. Hence, there are higher incidences of false-positive readings on echocardiography [20]. A TRV of 3.0 m/sec is 3 standard deviations above the population mean and identifies approximately ¾ of patients with a mPAP ≥ 25 mmHg while a TRV ≥ 2.5 m/sec identifies groups with borderline pulmonary