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Review Article

# Pathophysiology and Risk Factors of Pulmonary Hypertension in Patients with Thalassemia

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## Abstract

Pulmonary hypertension (PH) is recently defined in terms of hemodynamic criteria by a mean pulmonary arterial pressure (mPAP) determined by right heart catheterization of more than 20 mm Hg at rest. It is considered the main cause of morbidity and mortality in patients with chronic hemolytic anemias including thalassemia. It results in right ventricular failure and premature unexpected death if left untreated. PH is classified according to the World Health Organization (WHO) into five groups. Thalassemia is included within group 5 PH which occurs due to an unclear and/or multifactorial etiology. The occurrence of PH in thalassemia patients has a bad impact on the prognosis of the disease and on the survival in those patients. The pathogenesis of PH in thalassemia patients is complex and multi-factorial. It is assumed to be due to multiple overlapping pathogenic mechanisms including chronic hemolysis, inflammation, oxidative stress, decreased nitric oxide (NO) bioavailability, iron overload due to frequent repeated blood transfusion, hypercoagulability, erythrocyte dysfunction due to splenectomy, and chronic tissue hypoxia resulting from anemia leading to high cardiac output state and increased pulmonary vascular resistance.

**Keywords:** Pulmonary hypertension, Thalassemia**,** Iron overload, Splenectomy

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## Introduction

Thalassemia syndromes are the most common hemoglobin defect disorder in the world [1] They are inherited autosomal recessive diseases that occur as a result of defective synthesis of α or β subunits of globin chain of hemoglobin [2] They are classified according to the type of affected globin chains (α or β). The most common types of thalassemia include α- & β-thalassemia, and sickle cell thalassemia [3] The complete or partial defect in β-chain synthesis leads to α-chains overproduction in red blood cells (RBCs) precursors accelerating their apoptosis and subsequent hemolysis [4] Conversely, α-chains absence in α-thalassemia leads to relative overproduction of β chains impairing oxygen delivery to tissues due to impaired oxygen dissociation from hemoglobin [5] There are three clinical phenotypes of β-thalassemia including thalassemia major, minor, and intermedia. Anemia in β-thalassemia patients worsen with time if left without treatment leading to early death (6) resulting from high cardiac output heart failure [7] Pulmonary hypertension (PH) is considered one of the major cardiac complications in those patients which may lead to right-sided heart failure and unexpected death if left untreated. PH occurs mainly in patients with β-thalassemia major & intermediate. On the other hand, the occurrence of PH in α-thalassemia is very rare [8] PH is recently defined in terms of hemodynamic criteria by a mean pulmonary arterial pressure (mPAP) determined by right heart catheterization of more than 20 mm Hg at rest [9] It is classified according to the World Health Organization (WHO) into five groups [10] Thalassemia is included within group 5 PH which occurs due to an unclear and/or multifactorial etiology. The main hallmark of PH in patients with β-thalassemia is precapillary PH or pulmonary arterial hypertension (PAH) [11] PAH is a progressive dis-

ease .(12) and considered the main cause of morbidity and mortality in those patients .(13)

## Pathophysiology

The occurrence of PH in β-thalassemia patients is mostly multi-factorial due to multiple overlapping pathogenic mechanisms including chronic hemolysis, inflammation, oxidative stress, decreased nitric oxide (NO) bioavailability, iron overload due to frequent repeated blood transfusion, , hypercoagulability .(14) and erythrocyte dysfunction due to splenectomy .(8) and chronic tissue hypoxia resulting from anemia leading to high cardiac output.

## 1- Chronic hemolysis:

Hemolysis plays a significant role in the development of PH in patients with β-thalassemia because free hemoglobin produced from chronic hemolysis inactivates the intrinsic vasodilator NO and counteracts its vasodilator effect on the pulmonary circulation .(15) Furthermore, chronic hemolysis releases arginase enzyme leading to depletion of L-arginine .(8) Thus, increased arginase activity particularly converts L-arginine to ornithine instead of NO leading to inhibition of NO synthesis. Excess arginase action and low arginine bioavailability were demonstrated in thalassemia patients at higher risk for PH .(16) Moreover, hemolysis and decreased NO bioavailability results in platelets activation and aggregation, endothelial dysfunction, and increased oxidative stress leading to vascular tissue damage, vascular remodeling, and increased risk of intravascular thrombosis .(17) Also, hemolysis increases the release of the vasopressor endothelin-1 and results in a diffuse elastic tissue defect leading to vasculopathy .(18) Anemia and associated chronic tissue hypoxia increase cardiac output and amplify vasoconstriction of pulmonary capillaries resulting in increased pulmonary vascular resistance (PVR) .(19)

## 2- Iron overload:

Iron overload occurs mainly in patients with transfusion-dependent β-thalassemia major due to frequent repeated blood transfusion therapy in those patients leading to secondary hemochromatosis. It has a key role in the development of PH in patients with thalassemia through different mechanisms. It increases oxidative stress leading to vascular tissue injury and endothelial dysfunction .(20) Excessive iron deposition in myocardial tissue leads to myocardial fibrosis resulting in both right & left cardiac dysfunction and failure .(21) Thus, a significant high myocardial iron burden as shown by cardiac magnetic resonance imaging is a major cause of left ventricular dysfunction and left sided heart failure in those patients .(22) Furthermore, excess hemosiderin pulmonary deposits lead to fibrosis and stiffening of pulmonary capillary wall resulting in increased PVR .(23) Also, iron overload leads to liver fibrosis & cirrhosis particularly in patients with hepatitis C virus leading to portal hypertension and high probability of thrombosis and PH .(24)

## 3- Splenectomy:

Splenectomy is considered an important risk factor in the development of PAH .(25) because the spleen filters the hemolysed erythrocytes and other blood cells. Absence of this action leads to thrombocytosis, platelets activation, aggregation of atypical RBCs, and release of prothrombotic substances including products of RBCs breakdown in the circulation .(26) Splenectomy also results in release of immature nucleated RBCs which show enhanced expression of adhesion molecules .(27) All these factors are thought to enhance the thrombogenic effect especially in the presence of hypercoagulable state, endothelial dysfunction, and low NO bioavailability leading to an increased susceptibility to intravascular thrombosis causing remodeling within the pulmonary vasculature resulting in PAH .(8) Moreover, there is a significant association between splenectomy and the occurrence of PH in β-thalassemia patients as evidenced by multiple previous studies.

## 4- Hypercoagulable state:

Hypercoagulability is one of the well-known complications in patients with β-thalassemia.(28) leading to thromboembolic events such as deep-vein thrombosis, pulmonary embolism, and in-situ thrombosis which are more common in splenictomized patients with transfusion-independent thalassemia intermedia than in patients with transfusion-dependent thalassemia major .(29) The incidence of clinically obvious thromboembolic events in those patients is 1-4%. The majority of them occur at an age before 30 years.(30) Endothelial dysfunction, oxidative stress, vasculopathy, platelets activation and aggregation, abnormal erythrocytes aggregation, abnormal circulating erythrocyte breakdown products, splenectomy, and some coexistent inherited thrombophilia such

as proteins C, S and anti-thrombin III deficiency are all contributing factors in the pathogenesis of chronic hypercoagulable state and thromboembolism in β-thalassemia patients. (31&32)

All these above pathophysiological mechanisms are responsible for the occurrence of PH in patients with thalassemia in an overlapping manner. Hemolysis seems to be the main pathogenesis of PH in non-transfusion dependent patients with thalassemia intermedia, while chronic iron overload is the main pathophysiological factor in patients with thalassemia major receiving chronic repeated blood transfusion .(33)

## Risk factors

There are multiple risk factors shown to be implicated in the occurrence of PH in β-thalassemia patients including older age, extensive hemolysis, chronic iron overload evidenced by serum ferritin level of more than 800 microgram/L,(34) splenectomy,(35) hepatitis C, non-transfusion dependent thalassemia, past history of venous thromboembolic events, marked peripheral nucleated erythrocytosis $\geq 300\times10^6$/L, and thrombocytosis $\geq 500\times10^9$/L .(11) PH is five times more common to occur in patients with thalassemia intermedia than in thalassemia major patients .(36)

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