Saudi Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension: Pulmonary hypertension associated with hemolytic anemia

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Abstract:

Hereditary hemoglobin disorders affecting the globin chain synthesis namely thalassemia syndromes and sickle cell disease (SCD) are the most common genetic disorders in human. Around 7% of the world population carries genes for these disorders, mainly the Mediterranean Basin, Middle and Far East, and Sub-Saharan Africa. An estimated 30 million people worldwide are living with sickle cell disease, while 60-80 million carry beta thalassemia trait. About 400,000 children are born with severe hemoglobinopathies each year.

Cardiovascular complications of hemoglobinopathies include left and right ventricular (RV) dysfunction, arrhythmias, pericarditis, myocarditis, valvular heart disease, myocardial ischemia, and notably pulmonary hypertension (PH).

Because of a unique pathophysiology, pulmonary hypertension associated with hemolytic disorders was moved from WHO group I to group V PH diseases. Treatment strategies are also unique and include blood transfusion, iron chelation, hydroxyurea, and oxygen therapy. The role of PH-specific agents has not been established.

Key words:

Hemolysis, pulmonary hypertension, sickle cell anemia, thalassemia, Saudi association for pulmonary hypertension guidelines

Hereditary hemoglobin disorders affecting the globin chain synthesis namely thalassemia syndromes and sickle cell disease (SCD) are the most common genetic disorders in human. Around 7% of the world population carries genes for these disorders, mainly the Mediterranean Basin, Middle and Far East, and Sub-Saharan Africa. An estimated 30 million people worldwide are living with SCD, while 60-80 million carry beta thalassemia trait. About 400,000 children are born with severe hemoglobinopathies each year. Cardiovascular complications of hemoglobinopathies include left and right ventricular (RV) dysfunction, arrhythmias, pericarditis, myocarditis, valvular heart disease, myocardial ischemia, and notably pulmonary hypertension (PH). PH associated with hemoglobinopathies is the main cause of morbidity and mortality in this group of the population.[1-10] Several studies using tricuspid-valve regurgitant velocity (TRV) on Doppler echocardiography of at least 2.5 m/s to diagnose PH have put the prevalence of PH at 20-30% in SCD and 10-75% in thalassemia syndromes. In a series of 65 patients with SCD in a tertiary care Saudi hospital, echocardiographic evidence of PH was present in 38% of patients.[11] The prevalence of PH in other hemolytic disorders, such as hereditary spherocytosis and stomatocytosis, paroxysmal nocturnal hemoglobinuria, microangiopathic hemolytic anemia, and pyruvate kinase deficiency are not well-studied [Table 1]. It is believed that hemolytic disorders both acute and chronic are associated with PH.[10,12,13] In a longitudinal study, Ataga *et al*. followed patients with SCD whose initial screening had normal TRV over 3 years. A repeat echocardiography showed that 13% had developed echocardiographic evidence of PH suggesting incidence of about 4%/year.[14]

Although studies using TRV on Doppler echocardiography for diagnosis of PH have shown a high prevalence rate in patient with hemoglobinopathies, there appears to be a significant false positive rate as shown by Parent *et al*., who studies 398 patients with SCD, of which 109 patients (27%) had PH based on TRV >2.5 m/s. Ninety-six of these patients underwent right heart catheterization (RHC). Only 6% of these patients were found to have PH based on hemodynamic criteria.[15] Furthermore, RHC is not only an important tool in diagnosing PH, it also distinguishes precapillary PH from postcapillary PH, which is caused by left heart disease and frequently seen in hemolytic anemia.[16]

Pulmonary hypertension associated with chronic hemolytic anemia was classified as

Group 1 with a subcategory of associated pulmonary arterial hypertension in the 4th PH World Congress.[17] However, a new proposed NICE (5th World Congress) classification has moved this category of PH to Group 5 due to its complex nature, as shown in Table 2.[18]

Pathophysiology

The pathophysiology of PH in SCD and other chronic hemolytic disorders is complex. The common link for development of PH in all hemolytic disorders is probably the chronic hemolysis, as shown in Figure 1. Several studies have shown a strong association between the severity of hemolysis and development of PH.[19-21] Free hemoglobin released during hemolysis scavenges the intrinsic vasodilator nitric oxide (NO) and red cell breakdown releases arginase, which is an enzyme responsible for depletion of L-arginine, a substrate for NO synthesis. NO is one of the most potent vasodilators known and is an essential tool for vascular homeostasis. It plays an important role in the maintenance of vasomotor tone, limits platelet aggregation and ischemia-reperfusion injury, modulates endothelial proliferation, and has anti-inflammatory properties. Inactivation and reduced synthesis of NO leads to impaired NO dependent vasodilatation of pulmonary vasculature. Arginase is also responsible for altered metabolism of L-arginine to L-ornitine resulting in the synthesis of L-proline, which contributes to the smooth muscle proliferation and collagen synthesis leading to vascular remodeling and intimal thickening.[10,13,19,22-25]

There is an increased risk of thrombosis as factors released during red cell destruction leads to platelet activation, thrombin generation, and tissue factors activation leading to obliterative pulmonary vasculopathy. Hypercoagulable state develops from a variety of causes in these patients, including red cell precoagulant surface, genetic coagulation defects, splenectomy, endothelial dysfunction, and vaculopathy. Thromboembolic complications including pulmonary emboli and *in situ* thrombi have been reported in patients with hemoglobinopathy.[25-31] Since many patients with hemoglobinopathies have asplenia either due to auto or surgical splenectomy, the role of splenectomy as a risk factor for development of PH is well-established. Spleen plays an important role in removal of senescent and damaged red cells, and hence, its absence leads to platelet activation promoting microthromosis of pulmonary circulation and red cell adhesion to the capillary endothelial lining leading to vascular obliteration.[32-35] There is a role of endothelin pathway in development of PH in hemolytic disorders as hemolysis induces increased endothelin-1 mediated responses leading to pulmonary vasoconstriction. It has been shown that plasma endothelin-1 levels are increased in patients with SCD both in steady state and in sickle cell crisis.[36] Red cells in patients with hemoglobinopathies have increased concentrations of reactive oxygen species, such as superoxide, which can disrupt NO hemostasis by scavenging NO in pulmonary vascular system due to oxidative stress. As the glutathione buffering system is overwhelmed by oxidative stress, the red cells in these patients are more prone to hemolysis. It has been shown that erythrocyte glutathione depletion is associated with severity of PH in SCD.[37-40] Pulmonary complications in hemoglobinopathies, especially SCD, are linked to dysregulated arginine metabolism. Compromised oxygenation leads to increased sickling and vice versa.

Table 1: Hemolytic disorders associated with PH

Hemolytic disorders associated with PH
Thalassemia syndromes
Sickle cell disease
G6PD deficiency
Hereditary spherocytosis
Hereditary stomatocytosis
Paroxysmal nocturnal hemoglobinuria
Hb-mainz hemolytic anemia
Alloimmune hemolytic anemia
Pyruvate kinase deficiency
Microangiopathic hemolytic anemia
Evan's syndrome

G6PD = Glucose-6-phosphate dehydrogenase, PH = Pulmonary hypertension

Table 2: WHO Group 5

PH with unclear and/or multifactorial mechanisms
5.1 Hematological disorders:
5.1.1 Chronic hemolytic anemia
5.1.2 Myeloproliferative disorders
5.1.3 Splenectomy
5.2 Systemic disorders:
5.2.1 Sarcoidosis
5.2.2 Pulmonary Langerhans cell histiocytosis
5.2.3 Lymphangioleiomyomatosis
5.2.4 Neurofibromatosis
5.2.5 Vasculitis
5.3 Metabolic disorders:
5.3.1 Glycogen storage disease
5.3.2 Gaucher disease
5.3.3 Thyroid disorders
5.4 Others:
5.4.1 Tumoural obstruction
5.4.2 Fibrosing mediastinitis
5.4.3 Chronic renal failure on dialysis
5.4.4 Segmental PH (Pediatric classification)

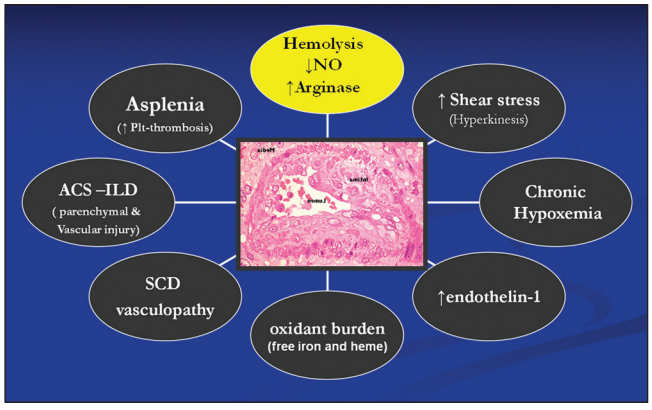

Figure 1: Pathophysiology of pulmonary hypertension in hemoglobinopathies

Chronic lung injury leads to pulmonary fibrosis and chronic hypoxemia, which in turn can cause increased pulmonary vascular resistance (PVR) and PH. There is probably no strong association between the number of episodes of acute chest syndrome and development of PH, as it occurs with equal prevalence in patients with thalassemia who do not develop acute chest syndrome.[19,41] Pulmonary venous hypertension due to left heart dysfunction is not uncommon in patients with hemoglobinopathies. Even in well-treated patients with thalassemia major, 7% were found to have systolic dysfunction, while 38% had diastolic dysfunction. In addition, mitral valve disease is much more common in these patients than in the normal population. Left heart disease in hemoglobinopaties is due to multiple factors, including iron overload, high output cardiac state, myocarditis, and elastic tissue defect. Iron overload not only lead to left heart dysfunction, it also causes liver disease contributing further to the development of PH due to liver cirrhosis.[6,42-44] In short, the pathobiology of PH in hemolytic disorders is a rainbow of many colors. Mechanisms like NO depletion, dysregulated arginine metabolism, oxidative stress and hypercoagulable state result in pulmonary vasoconstriction, endothelial proliferation and hyperplasia, and *in situ* thrombi. However, the development of plexiform pulmonary arteriopathy in this group of patients has been recently challenged, as most reported plexiform lesions in old studies where indeed organized thrombi.

In reality, PH in hemolytic disorders is mainly a combination of precapillary and postcapillary PH and while a small proportion of patients have hypoxia-induced PH and thromboembolic PH, as shown in Figure 2.[19,45-49]

Clinical Features and Diagnosis

Dyspnea, which is a typical symptom associated with PH, is very common in patients with hemoglobinopathies due to anemia. It is very important to have an index of suspicion in these patients and perform screening echocardiography. Even a mild degree of PH in these patients is poorly tolerated due to chronic anemia, which results in very high cardiac output usually in the range of 10 L/min resulting in significant morbidity and possibly mortality.

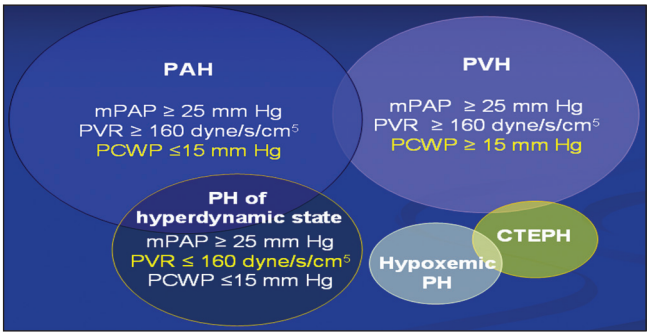

Figure 2: Different types of pulmonary hypertension in patients with hemolytic disorders

Patients with SCD and PH (mean pulmonary artery pressure [mPAP] of 36 ± 1.5 mmHg) when compared with patients with normal PAP are found to have walked significantly lower distance on 6-min walk test (435 ± 31 vs. 320 ± 20 m; $P = 0.002$) and had lower maximum oxygen uptake (50 ± 3% vs. 41 ± 2% of normality; $P = 0.02$).[16] PVR in patients with SCD sharply rises with exercise, suggesting that pulmonary vascular disease contributes to functional impairment in this group of patients.[49] Patients with hemoglobinopathies are more symptomatic as compared to patients with idiopathic pulmonary artery hypertension (IPAH) despite lower mPAP and PVR. The workup of exercise intolerance should also include aggressive search for other conditions contributing to PH such as chronic liver disease, HIV, iron overload, sleep apnea, and thromboembolism.[50]

Doppler echocardiography is an excellent screening tool for cardiovascular complications in patients with hemoglobinopathies.[24] It may overestimate PAP resulting in false positive results especially in patients with hemoglobinopathies where several factors lead to high output state. RHC in patients with hemoglobinopathies is recommended in making a diagnosis of precapillary PH defined by mPAP ≥25 mmHg and pulmonary arterial wedge pressure (PAWP) <15 mmHg. In a multi-center study mentioned earlier, the prevalence of PH in SCD by RHC was 6%, while only about 2% patients had true precapillary PH with a PAWP of 15 mmHg or less. The positive predictive value of echocardiography for the detection of PH was only 25%.[15] A TRV of 2.5 m/s or higher on Doppler echocardiogram is a strong predictor of death in patients with SCD with about 40% mortality risk within 3 years of diagnosis.[51] Patients with SCD have a high-risk of death with mild elevation of pulmonary pressure as compared to patients with IPAH.[52] Several reports support the use of TRV of 2.5 m/s as a good threshold for intervention. About 10% of patients with SCD have TRV >3 m/s and a majority of these have mean PAP >25 mmHg on RHC.[13,16,19] Evidence of diastolic dysfunction on echocardiography is common in these patients, which is an independent mortality risk in patient with SCD. In a cohort of 141 patients with SCD, Sachdev *et al*. have reported a relative risk of death of 4.8 (95% confidence interval [CI], 1.9-12.1), whereas relative risk of death when both PH and diastolic dysfunction are present was 12.0 (95% CI, 3.8-38.1).[53] The N-terminal pro-brain natriuretic peptide (NT-pro-BNP) has been found to have a correlation with the severity of PAP and RV dysfunction in IPAH.[52] Levels of NT-pro BNP are also found to be higher in patients with sickle cell-induced PH and correlate directly with TRV.[54] An NT-pro-BNP level of 160 pg/mL or higher has a 78% positive predictive value for the diagnosis of PH and is an independent predictor of mortality with a risk ratio of 5.1 (95% CI, 2.1-12.5).[41]

Treatment

There are no specific treatment guidelines on the management of patients with hemoglobinopathy associated PH. It is essential that treatment of primary hemoglobinopathy should be maximized, hypoxia should be corrected by chronic oxygen use and associated complications like cardiopulmonary conditions should be treated appropriately. There are two aspects of management in these patients, mainly hemoglobinopathy specific treatment and PH-specific

treatment. Hemoglobinopathy specific treatment includes blood transfusion, iron chelation and hydroxyurea, while PH-specific therapy comprises of anticoagulation, diuretics, digoxin, oxygen, and PAH specific vasodilator agents. Chronic blood transfusion in patients with SCD has been shown to reduce the synthesis of sickle cells and its associated complications including pulmonary events and central nervous system vasculopathy.[55,56] Aggressive transfusion therapy and iron chelation in patients with thalassemia major has been shown to completely prevent the development of PH in one study.[42] Although transfusion therapy lower plasma free hemoglobin, which is an important trigger in development of PH in these patients, there are no prospective studies evaluating its efficacy to decrease PH in this group of patients. There are few case reports of improvement of TRV with transfusion therapy;[21] and a retrospective study of SCD patients who were transfused has shown significantly lower TRV as compared to those who were not transfused.[57] The aim of transfusion therapy is to maintain Hb level of ≥8 g/dl and HbS level of <40%.

Although studies have not shown a conclusive relationship between hydroxyurea use and reduction of TRV in patients with SCD,[19,41,58,59] hydroxyurea is a useful treatment tool. It helps to reduce hemolysis, increase hemoglobin, induces NO in endothelial cells, improves clinical symptoms, reduces the requirement for blood transfusion, and prevent acute episodes that exacerbate PH and potentially decrease overall mortality.[60,61] Two small case series have shown reduction in TRV with the use of hydroxyurea.[62,63] In a recent study of 584 patients with thalassemia intermedia, optimum therapy involving blood transfusion, chelation therapy and hydroxyurea has found that this strategy is protective against development of PH.[64]

Anticoagulation in IPAH has been shown to decrease mortality,[65-67] however, the potential benefit of warfarin in hemoglobinopathy associated PH has to be weighed against the risk of hemorrhagic complications. It has been recommended that patients with severe SCD associated PH may be considered for oral anticoagulation if there is no contraindication. However, the conclusive answer about this question will be answered once the ongoing randomized clinical trial is completed.

Due to the old belief that the pathobiological pathways of plexiform lesion similar to PAH also play a role in hemoglobinopathy associated PH, vasodilator therapies including prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors have been tried in these patients. As NO depletion is a critical factor in the development of PH in SCD patients, chronic NO administration would be an attractive method of therapy. However, chronic NO treatment is not practical for general use as the delivery system is very complicated and expensive.[47,68] L-arginine improves NO bioavailability and has been shown to decrease systolic PAP in patients with SCD.[69-71] Use of L-carnitine for 3 months in a case series of 32 patients with beta thalassemia major showed a significant reduction in systolic PAP.[72]

Targeted PH-specific therapy has certain setbacks in patients with hemoglobinopathies, especially SCD. In addition to their general adverse profile, there are specific side-effects that can interfere negatively with the pathophysiological aspects of SCD and other hemoglobinopathies [Table 3].

Phosphodiesterase-5 inhibitors have been tried in few small case series with positive results. Derchi *et al*. have reported 7 patients, 4 with thalassemia intermedia, 2 with thalassemia major and 1 with sickle thalassemia. Treatment with sildenafil in these patients who had severe PH improved 6-min walk distance (6MWD) and the modified NYHA functional class and decreased TRV.[73] Another small study of sildenafil use in 12 patients with SCD associated PH has shown that sildenafil use for a mean of 6 months was resulted in improved 6MWD, decreased TRV, mPAP and NT-pro BNP levels.[74] Another case series of 14 patients in which sildenafil and L-arginine was used has shown a significant improvement in 6MWD and decreased TRV with sildenafil, but not L-arginine.[75] A multi-center randomized double-blind trial (walk-PHaSST trial) was terminated in July 7, 2009 because of the increased occurrence of painful crises in the sildenafil arm and the lack of benefit from this agent in patients who completed the study. Hence, it is recommended that phosphodiesterase-5 inhibitors should not be considered as first-line agents for the treatments of PH in patients with SCD in the light of walk-PHaSST study.

A clinical trial of use of endothelin receptor antagonists (bosentan or ambrisentan) as monotherapy or in combination with sildenafil in 14 patients with SCD-PH showed improvement in 6MWD and a reduction in TRV, mPAP, and NT-pro-BNP levels.[76]

A randomized, double-blind, multi-center trial to assess the efficacy, safety, and tolerability of bosentan in patients with symptomatic pulmonary arterial hypertension associated with SCD (ASSET-1 and ASSET-2) studies were prematurely terminated because of slow site activation and patient recruitment.

ASSET-1 was for patients with precapillary PH while ASSET-2 for pulmonary venous hypertension. In a limited sample of 26 patients, bosentan use for 16 weeks was well tolerated and there was a nonsignificant increase in cardiac output and decrease in PVR. Because of the limited sample size, efficacy endpoints were not formally analyzed.[77] Acute administration of intravenous eposprostenol in patients with SCD-PH has shown to decrease PVR from 271 dyne/s/c^5 to 170 dyne/s/c^5 and to increase cardiac output from 7.1 l/min to 9.1 l/min. There are no studies on chronic use of prostanoid analogues in this group of patients.[52]

Conclusion

Cardiopulmonary complications associated with SCD and other hemoglobinopathies are major causes of morbidity and mortality. PH in these patients has a complex and multifactorial pathophysiology. Many disease-related mechanisms, especially

Table 3: Adverse effects of PH-specific agents in SCD

Therapeutic agent	Prostanoids	PDE-5 inhibitors	ERA
Adverse effects	Worsening of hyper-dynamic state and heart failure	Priapism ACS	Liver toxicity Worsening anemia

ERA = Endothelin receptors antagonists, PDE = Phosphodiesterase, ACS = Acute chest syndrome, PH = Pulmonary hypertension, SCD = Sickle cell disease

hemolysis, play an important role in the development of PH. Treatment strategies include disease specific modalities, such as blood transfusion, iron chelation, hydroxyurea, and oxygen therapy that may prevent the development and progression of PH. The role of PH-specific agents is not established. Threshold of screening for PH in this group of patients should be low, so that the treatment can be optimized in order to improve the quality of life and prolong survival.

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