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 hemoglobinopaties each year.

Cardiovascular complications of hemoglobinopathies include left and right ventricular (RV) dysfunction, arrhythmias, pericarditis, myocardiitis, 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 sickle cell disease, while 60-80 million carry beta thalassemia trait. About 400,000 children are born with severe hemoglobinopaties each year. Cardiovascular complications of hemoglobinopathies include left and right ventricular (RV) dysfunction, arrhythmias, pericarditis, myocardiitis, 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. 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.

### 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. 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.

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 vasculopathy. Thromboembolic complications including pulmonary emboli and in situ thrombi have been reported in patients with hemoglobinopathy. 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.

### 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-main 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

Figure 2: Table of PH groups and associated conditions

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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. 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 hemoglobinopathies 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. In 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.

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.

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). PVR in patients with SCD sharply rises with exercise, suggesting that pulmonary vascular disease contributes to functional impairment in this group of patients. 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.

Doppler echocardiography is an excellent screening tool for cardiovascular complications in patients with hemoglobinopathies. 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%. 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. Patients with SCD have a high-risk of death with mild elevation of pulmonary pressure as compared to patients with IPAH. 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. 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 is 12.0 (95% CI, 3.8-38.1). 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. Levels of NT-pro BNP are also found to be higher in patients with sickle cell-induced PH and correlate directly with TRV. 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).

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...
calcification of plexiform lesion similar to PAH also play a role in vasculopathy. Many disease-related mechanisms, especially pathobiological pathways of plexiform lesion similar to PAH also play a role in vasculopathy. Many disease-related mechanisms, especially

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 | Liver toxicity |
|                  | ACS         |                | Worsening anemia |

This table lists the adverse effects of prostanoids, PDE-5 inhibitors, and ERA (Endothelin receptor antagonists) in patients with SCD. Worsening of hyper-dynamic state and heart failure can be seen with prostanoids, priapism with ERA, and liver toxicity with PDE-5 inhibitors. Worsening anemia can be observed with both ERA and PDE-5 inhibitors.

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. 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. 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. A multi-center randomized double-blind trial (walk-PHaSST trial) was terminated in July 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.

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. Acute administration of intravenous epoprostenol in patients with SCD-PH has shown to decrease PVR from 271 dyne/s/cm² to 170 dyne/s/cm² 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.

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].

Anticoagulation in IPAH has been shown to decrease mortality, 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. It has been recommended that patients with severe SCD associated PH may be considered for oral anticoagulation if there is no contraindication.

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, and a retrospective study of SCD patients who were transfused has shown significantly lower TRV as compared to those who were not transfused. 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, hydroxyurea is a useful treatment tool. It helps to reduce hemolysis, increase hemoglobin, induces NO in endothelial cells, improves clinical symptoms, reduces the risk for blood transfusion, and prevent acute episodes that exacerbate PH and potentially decrease overall mortality. Two small case series have shown reduction in TRV with the use of hydroxyurea. 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.

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Due to the old belief that the pathobiological pathways of plexiform lesion similar to PAH also play a role in hemoglobinopathy associated PH, as also play a role in hemoglobinopathy associated PH, as well as 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. Aggressive transfusion therapy and iron chelation in patients with thalassemia major has been shown to completely prevent the development of PH in one study. 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, and a retrospective study of SCD patients who were transfused has shown significantly lower TRV as compared to those who were not transfused. The aim of transfusion therapy is to maintain Hb level of ≥8 g/dl and HbS level of <40%.

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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...
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.

References

1. Alabdulaali MK. Sickle cell disease patients in eastern province of Saudi Arabia suffer less severe acute chest syndrome than patients with African haplotypes. Ann Thorac Med 2007;2:158-62.

2. Weatherall DJ, Clegg JB. Inherited haemoglobin disorders: An increasing global health problem. Bull World Health Organ 2001;79:704-12.

3. Cavalli-Sforza LL, Menozzi P, Piazza A. The History and Geography of Human Genes. Princeton, NJ: Princeton University Press; 1994.

4. Weatherall DJ. The thalassaemias. BMJ 1997;314:1675-8.

5. Sutton LL, Castro O, Cross DJ, Spencer JE, Lewis JF. Pulmonary hypertension in sickle cell disease. Am J Cardiol 1994;74:626-8.

6. Aessopos A, Farmakis D, Karagiorga M, Voskaridou E, Loutradi A, Hatzilamia A, et al. Cardiac involvement in thalassemia intermedia: A multicenter study. Blood 2001;97:3411-6.

7. Derchi G, Fonti A, Galliera EO, Cappellini MD, Turati F, et al. Pulmonary hypertension in patients with thalassemia major. Am Heart J 1997;134:532-7.

8. Du ZD, Roguin N, Milgram E, Saab K, Koren A. Pulmonary hypertension in patients with sickle cell disease. Am J Hematol 2001;79:704-12.

9. Grisaru D, Rachmilewitz EA, Mosseri M, Gotsman M, Lafair JS, Okon E, et al. Cardiopulmonary assessment in beta-thalassemia major. Chest 1990;98:1138-42.

10. Barnett CF, Hsue PY, Machado RF. Pulmonary hypertension: An increasingly recognized complication of hereditary hemolytic anemias and HIV infection. JAMA 2008;299:324-31.

11. Aleem A, Jahangir A, Owais M, Al-Momen A, Al-Diab A, Abdulkarim H, et al. Echocardiographic abnormalities in adolescent and adult Saudi patients with sickle cell disease. Saudi Med J 2007;28:1072-5.

12. Connor P, Veys P, Amrolia P, Haworth S, Ashworth M, Parent F, et al. Pulmonary hypertension in patients with thalassemia major. Am Heart J 1997;134:532-7.

13. Aessopos A, Farmakis D, Karagiorga M, Voskaridou E, Loutradi A, Hatzilamia A, et al. Cardiac involvement in thalassemia intermedia: A multicenter study. Blood 2001;97:3411-6.

14. Farmakis D, Aessopos A. Pulmonary hypertension associated with hemoglobinopathies: Prevalent but overlooked. Circulation 2011;123:1227-32.

15. Parent F, Bachir D, Inamo J, Lionnet F, Driss F, Loko G, et al. A hemodynamic study of pulmonary hypertension in sickle cell disease. N Engl J Med 2011;365:44-53.

16. Anthi A, Machado RF, Jison ML, Taveira-Dasilva AM, Rubini LJ, Hunter L, et al. Hemodynamic and functional assessment of patients with sickle cell disease and pulmonary hypertension. Am J Respir Crit Care Med 2007;175:1272-9.

17. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009;54 1 Suppl:S43-54.

18. Simonneau G, Gatouilis MA, Adatia I, Celermager D, Denton C, Ghofrani A, et al. Updated clinical classification of pulmonary hypertension. Am J Cardiol 2013;62 25 Suppl:S34-41.

19. Gladwin MT, Sachdev V, Jison ML, Shizukuda Y, Plehn JF, Minter K, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. N Engl J Med 2004;350:886-95.

20. Kato GJ, McGowan V, Machado RF, Little JA, Taylor J 6th, Morris CR, et al. Lactate dehydrogenase as a biomarker of hemolysis-associated nitric oxide resistance, priapism, leg ulceration, pulmonary hypertension, and death in patients with sickle cell disease. Blood 2006;107:2279-85.

21. Kato GJ, Onyekwere OC, Gladwin MT. Pulmonary hypertension in sickle cell disease: Relevance to children. Pediatr Hematol Oncol 2007;24:159-70.

22. De Castro LM, Jonassaint JC, Graham FL, Ashley-Koch A, Telen MJ. Pulmonary hypertension associated with sickle cell disease: Clinical and laboratory endpoints and disease outcomes. Am J Hematol 2008;83:19-25.

23. Kato GJ, Gladwin MT, Steinberg MH. Deconstructing sickle cell disease: Reappraisal of the role of hemolysis in the development of clinical subphenotypes. Blood Rev 2007;21:37-47.

24. Rother RP, Bell L, Hillmen P, Gladwin MT. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: A novel mechanism of human disease. JAMA 2005;293:1653-62.

25. Villagra J, Shiva S, Hunter LA, Machado RF, Gladwin MT, Kato GJ. Platelet activation in patients with sickle disease, hemolysis-associated pulmonary hypertension, and nitric oxide scavenging by cell-free hemoglobin. Blood 2007;110:2166-72.

26. Hagger D, Wolf S, Owen J, Samson D. Changes in coagulation and fibrinolysis in patients with sickle cell disease compared with healthy black controls. Blood Coagul Fibrinolysis 1995;6:93-9.

27. Ataga KI, Moore CG, Hillery CA, Jones S, Whinna HC, Strayhorn D, et al. Coagulation activation and inflammation in sickle cell disease-associated pulmonary hypertension. Haematologica 2008;93:20-6.

28. van Beers EJ, Sprook HM, Ten Cate H, Duits AJP, Brandjes DP, van Esser JW, et al. No association of the hypercoagulable state with sickle cell disease related pulmonary hypertension. Haematologica 2008;93:e42-4.

29. Westerman M, Pizzy A, Hirschman J, Cerino M, Weil-Weiner Y, Ramotar P, et al. Microvesicles in haemoglobinopathies offer insights into mechanisms of hypercoagulability, haemolysis and the effects of therapy. Br J Haematol 2008;142:126-35.

30. Aessopos A, Kati M, Farmakis D. Heart disease in thalassemia intermedia: A review of the underlying pathophysiology. Haematologica 2007;92:658-65.

31. Sonakul D, Fucharoen S. Pulmonary thromboembolism in thalassemic patients. Southeast Asian J Trop Med Public Health 1992;23 Suppl 2:225-8.

32. Atichartakarn V, Likittanasombat K, Chuncharunee S, Chandanamaththa P, Worapongpaiboon S, Angchaisukpiri P, et al. Pulmonary arterial hypertension in previously splenectomized patients with beta-thalassemia disorders. Int J Hematol 2003;78:139-45.

33. Chou R, DeLoughery TG. Recurrent thromboembolic disease following splenectomy for pyruvate kinase deficiency. Am J Hematol 2001;67:197-9.

34. Hayag-Barin JE, Smith KE, Tucker FC Jr. Hereditary spherocytosis, thrombocytosis, and chronic pulmonary emboli: A case report and review of the literature. Am J Hematol 1998;57:82-4.

35. Atichartakarn V, Angchaisukpiri P, Aryurachai K, Chuncharunee S, Thakkinstian A. In vitro platelet activation and hyperaggregation in hemoglobin E/beta-thalassemia: A consequence of splenectomy. Int J Hematol 2003;77:299-303.

36. Rybicki AC, Benjamin LJ. Increased levels of endothelin-1 in plasma of sickle cell anemia patients. Blood 1998;92:2594-6.

37. Ergul S, Brunson CY, Hutchinson J, Tawfik A, Kutlar A, Webb RC, et al. Vasoactive factors in sickle cell disease: In vitro evidence for endothelin-1-mediated vasoconstriction. Am J Hematol 2004;76:245-51.
38. Hebbel RP, Eaton JW, Balasingam M, Steinberg MH. Spontaneous oxygen radical generation by sickle erythrocytes. J Clin Invest 1982;70:1253-9.

39. Chakraborty D, Bhattacharyya M. Antioxidant defense status of red blood cells of patients with beta-thalassemia and Ebeta-thalassemia. Clin Chim Acta 2001;305:123-9.

40. Morris CR, Suh JH, Hagar W, Larkin S, Bland DA, Steinberg MH, et al. Erythrocyte glutamine depletion, altered redox environment, and pulmonary hypertension in sickle cell disease. Blood 2008;111:402-10.

41. Machado RF, Antbi A, Steinberg MH, Bonds D, Sachdev V, Kato GJ, et al. N-terminal pro-brain natriuretic peptide levels and risk of death in sickle cell disease. JAMA 2006;296:310-8.

42. Aessopos A, Farmakis D, Hatziliami C, Karabatsos F, Joussouf J, et al. Cardiac status in well-treated patients with thalassemia major. Eur J Haematol 2004;73:359-66.

43. Aessopos A, Farmakis D, Deftereos S, Tsironi M, Tassiopoulos S, Mouyssakis I, et al. Thalassemia heart disease: A comparative evaluation of thalassemia major and thalassemia intermedia. Chest 2005;127:1523-30.

44. Aessopos A, Farmakis D, Trompoukis C, Tsironi M, Mouyssakis I, Tsafarides P, et al. Cardiac involvement in sickle beta-thalassemia. Ann Hematol 2009;88:557-64.

45. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JW, et al. Task force on expert consensus documents on pulmonary hypertension. J Am Coll Cardiol 2009;53:1573-619.

46. Morris CR. Mechanisms of vasculopathy in sickle cell disease and thalassemia. Hematology Am Soc Hematol Educ Program 2008;177-85. doi: 10.1182/ashedducation-2008.1.177.

47. Reiter CD, Wang X, Tanus-Santos JE, Hogg N, Cannon RO 3rd, et al. Cell-free hemoglobin limits nitric oxide bioavailability in sickle-cell disease. Nat Med 2002;8:1383-9.

48. Morris CR, Kato GJ, Poljakovic M, Wang X, Blackwelder WC, Sachdev V, et al. Dysregulated arginine metabolism, hemolysis-associated pulmonary hypertension, and mortality in sickle cell disease. JAMA 2005;294:81-90.

49. Machado RF, Mack AK, Martyr S, Barnett C, Macarthur P, Sachdev V, et al. Severity of pulmonary hypertension during vaso-occlusive pain crisis and exercise in patients with sickle cell disease. Br J Haematol 2007;136:319-25.

50. McGoon M, Gutterman D, Steen V, Barst R, McCrory DC, Fortin TA, et al. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest 2004;126:14S-3.

51. Morris CR. Vascular risk assessment in patients with sickle cell disease. Haematologica 2011;96:1-5.

52. Castro O, Hoque M, Brown BD. Pulmonary hypertension in sickle cell disease: Cardiac catheterization results and survival. Blood 2003;101:1257-61.

53. Sachdev V, Machado RF, Shizukuda Y, Rao YN, Sidenko S, Ernst L, et al. Diastolic dysfunction is an independent risk factor for death in patients with sickle cell disease. J Am Coll Cardiol 2007;49:472-9.

54. Voskaridou E, Tsetsos G, Spyropoulou E, Christoulas D, Terpos E. Pulmonary hypertension in patients with sickle cell/beta thalassemia: Incidence and correlation with serum N-terminal pro-brain natriuretic peptide concentrations. Haematologica 2007;92:738-43.

55. Adams RJ, McKie VC, Hsu L, Files B, Vichinsky E, Pegelow C, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med 1998;339:5-11.

56. Pegelow CH, Adams RJ, McKie V, Abboud M, Berman B, Miller ST, et al. Risk of recurrent stroke in patients with sickle cell disease treated with erythrocyte transfusions. J Pediatr 1995;126:896-9.

57. Joyce K, Sable C, Martin B, et al. Pulmonary artery hypertension in children with sickle cell disease: Is chronic transfusion protective? Blood 2006;108:356a.
75. Little JA, Hauser KP, Martyr SE, Harris A, Maric I, Morris CR, et al. Hematologic, biochemical, and cardiopulmonary effects of L-arginine supplementation or phosphodiesterase 5 inhibition in patients with sickle cell disease who are on hydroxyurea therapy. Eur J Haematol 2009;82:315-21.

76. Minniti CP, Machado RF, Coles WA, Sachdev V, Gladwin MT, Kato GJ. Endothelin receptor antagonists for pulmonary hypertension in adult patients with sickle cell disease. Br J Haematol 2009;147:737-43.

77. Barst RJ, Mubarak KK, Machado RF, Ataga KI, Benza RL, Castro O, et al. Exercise capacity and haemodynamics in patients with sickle cell disease with pulmonary hypertension treated with bosentan: Results of the ASSET studies. Br J Haematol 2010;149:426-3.

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