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Thalassemia Associated Pulmonary Hypertension

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Abstract
Cardiac disease is the main cause of death in both forms of thalassemia; thalassemia major (TM) and thalassemia intermedia (TI). Pulmonary hypertension (PH) is one of the cardiopulmonary morbidities with high mortality that, if not treated, may trigger right-sided heart failure and premature death. PH is defined as a mean pulmonary artery pressure of ≥25 mmHg at rest or ≥30 mmHg during exercise. The prevalence of PH is known to be higher in TI than in TM. Moreover, the pathophysiology of PH in thalassemia appears to be sophisticated and complex. Risk factors for occurrence of PH consists of non-transfusion dependent thalassemia (NTDT), sub-optimally transfused transfusion dependent thalassemia (TDT), splenectomy, thrombocytosis, anemia, NRBC ≥ 300×10^6, iron accumulation, history of thrombosis and older age. Other parameters which aggravate the risk of PH include hemolysis, oxidative stress, hypoxemia, alteration of erythrocyte membrane, decline of nitric oxide biological availability, arginine abnormal regulation and arginase excess. The screening method for PH is Doppler echocardiography but the gold standard for detection of PH is right heart catheterization (RHC). Current medical therapeutic options in PH comprise hydroxyurea, L- Carnitine, sildenafil, calcium channel antagonists, endothelin 1-receptor blockers and prostacyclin agonists. The only curative surgical method for the refractory and severe cases of PH is pulmonary endarterectomy. In this article, the etiology, pathophysiology, diagnostic methods and novel therapies of thalassemia associated PH are discussed.
Key words: Cardiac, Pulmonary hypertension, Thalassemia.

Introduction

Thalassemia syndromes are the most common types of monogenic hemoglobinopathy in the world. The principal characteristic of this hemoglobin disorder is the defective synthesis of α or β globin subunits (1). The complete absence or severe reduction of β-chain synthesis results in overproduction of α chains in precursors of erythroid cells. The excess of α chains causes accelerated apoptosis of red blood cells and hemolysis (2). On the other hand, the absence of α chains leading to overproduction of β chains engenders impaired dissociation of oxygen from hemoglobin and disturbance of oxygen delivery to different tissues (3). The most critical part of management in thalassemia is chronic transfusion program and chelating therapy, and prevention of cardiac morbidity is the main effect of iron chelator drugs (4). Ineffective chelation results in iron overload in vital organs such as heart, liver, pancreas, kidneys, adrenal and pituitary glands. Cardiac involvement is the most important etiology of mortality in both forms of β-thalassemia major and intermedia.

One of the main complications of cardiac disease in thalassemic patients is pulmonary hypertension (PH) which might induce some devastating outcomes. PH may give rise to right-sided cardiac failure and unexpected death (5). Pulmonary hypertension can be detected in β thalassemia major (TM) and thalassemia intermediate (TI); however, the presence of PH in α thalassemia is extremely rare (6).

Iran is located on thalassemia belt with an

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approximately thalassemia gene prevalence rate of 4% (7). Fortunately, thalassemia preventing program has been initiated in Iran since 1997 hence leading to a marked decline in the birth rate of thalassemic newborns (8).

Definition of PH

The most important characteristic of the pulmonary arterial hypertension (PAH) in β thalassemia is precapillary PH without lung disease, left-sided heart disease and chronic thromboembolism (9). PH is defined as a mean pulmonary artery pressure of higher than 25 mmHg at rest or ≥ 30 mmHg during exercise (10). Also a tricuspid regurgitation velocity (TRV) greater than2.9 m/sec in general population measured by Doppler echocardiography and TRV more than 2.5 m/sec in a population with chronic hemolytic anemia such as thalassemia and sickle cell disease represent pulmonary hypertension (11). According to WHO functional classification, PH is classified in 5 groups. This classification was presented in the Fifth World Symposium on pulmonary hypertension in 2013. Previously, pulmonary hypertension during chronic hemolytic anemias was categorized into group 1, but recently it has been classified in group 5 (12). This group description consists of 5 classes:

Class 1: Pulmonary arterial hypertension including idiopathic PAH, heritable PAH , drug or toxin induced PAH and other situations such as connective tissue disorders, AIDS, portal hypertension, congenital heart disease and infection with *schistosomiases*.

Class 2: PH owing to left heart disease

Class 3: PH due to lung disorders or hypoxia

Class 4: Chronic thromboembolic pulmonary hypertension

Class 5: PH with undefined etiology

In this classification, disorders including thalassemia, sickle cell disease, splenectomy, sarcoidosis, glycogen storage disorders, granulomatous disease, thyroid disorder, tumoral obstruction and chronic renal failure have been classified as group 5 (12).

Pathophysiology

Two important contributory factors in the pathogenesis of PH are cardiac output and pulmonary vascular bed resistance. Pulmonary vascular dilatation can compensate for increased cardiac output, but in the presence of vascular bed resistance, cardiac output increases and exerts an influence on elevation of pulmonary arterial pressure. In thalassemic patients, tissue hypoxemia due to anemia, is the main cause of high cardiac output. Because of regular repeated transfusions, thalassemia major patients experience lower tissue hypoxia in comparison to intermediate forms. Moreover, other conditions such as liver damage, iron overload and extramedullary hematopoiesis may trigger an elevation in cardiac output (5). Multiple factors may contribute to increased pulmonary vascular bed resistance. Among these, decreased nitric oxide (NO) and arginine bioavailability play a crucial role. The principal function of NO is vasodilatation; therefore, its depletion engenders vasoconstriction. Chronic hemolysis produces free hemoglobin which assists in inactivating NO. On the other hand, NO production is inhibited by the release of arginine during hemolysis. In addition, L-arginine provides substrate for both NO synthase and arginase. Moreover, increased arginase activity advances the formation of ornithine rather than NO (6). In a recent study, Morris et al. demonstrated that in thalassemic patients, along with increased TRV, arginase activity elevates whereas arginine bioavailability declines (13). Hemolysis and reduced NO bioavailability may trigger activation of platelets, elevated oxidative stress ,impaired function of endothelial cells, and finally tissue injury in circulation (14). Also hemolysis may contribute to a diffuse elastic tissue defect

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in patients with thalassemia especially in TI patients. Endothelial dysfunction is a contributory factor for hypercoagulability and thrombus development through the pulmonary vascular bed (5). Additionally, marked hemostatic changes and hypercoagulable state have been detected in thalassemia syndromes (15). These alterations such as enhanced platelet activation and aggregation are more prominent in TI compared to TM. Also in several studies, a significant reduction in proteins C, S and anti-thrombin Ш have been shown (16-19). Further, thrombocytosis due to splenectomy can promote thromboembolic events in thalassemic patients. Thrombus formation in the pulmonary arterioles of splenectomized thalassemic patients can likely be associated with diminished vascular bed in pulmonary system and accordingly elevated risk of PH. Age-related respiratory dysfunction due to recurrent respiratory infection, chest wall deformities and hematopoietic mass in the thorax due to marrow expansion and extramedullary hematopoiesis may accentuate PH particularly in TI. Hypoxemia, anemia and the increased level of hemoglobin F (with high oxygen affinity) may induce vasoconstriction and elevation of pulmonary vascular resistance (5).
Regular transfusion in thalassemic patients prevents chronic tissue hypoxemia and hemolysis and therefore modifies PH by limiting NO bioavailability. Also regular transfusions reduce some pro-inflammatory hormones such as placental growth factor (PIGF) in the circulation (20).
The consequence of repeated transfusions is secondary hemochromatosis giving rise to impaired function of the left and right side of the heart. Moreover, excess iron accumulation in the lung parenchyma results in pulmonary fibrosis and arterial wall stiffening, which helps to increase pulmonary vascular bed resistance (6). The pathophysiology of PH in patients with TI and TM runs counter to each other. Hemolysis plays a significant role in non-transfused TI whereas hemosiderosis and oxidative stress are some critical factors in pathogenesis of TM that receive regular transfusions (10).

Incidence

The reported incidence of PH among TDT and NTDT is widely varied. Based on echocardiographic criteria, 40-50 % of TI and 10-75% of TM patients suffer from PH (6). In earlier studies, an extensive incidence of PH in TM (70-80%) has been reported although in some recent investigations, its incidence has significantly reduced (21). Documentation of PH by echocardiographic criteria induces overestimation of incidence among thalassemic patients (9). However, advances in management of thalassemia, such as transfusion protocols and chelation therapy, have led to a marked decline in the incidence of PH in patients with TDT and NTDT (21). Aessopos et al., in a study on 200 well-treated TM patients have reported no cases of PH (22). This can be ascribed to difficulty in differentiating thalassemia major from severe forms of thalassemia intermedia (23).
The differences in the prevalence of PH in various studies can likely be due to different screening cutoff values for identification of PH based on echocardiography (24). Also the prevalence of PH turned out to be significantly lower when confirmatory right heart catheterization has been employed (9).

Risk factors

There are multiple risk factors for occurrence of PH in β thalassemia such as NTDT, irregular transfusion in TDT, splenectomy, platelet count $\geq 500\times10^9$/ L, NRBC $\geq 300\times10^6$/L, hemoglobin level <9 gr/dL, marked iron deposition and history of thrombosis (9). Compared with thalassemia major patients, intermediate

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thalassemia cases are five times more likely to develop pulmonary hypertension (25).

Splenectomy is a documented factor in the pathogenesis of PH in thalassemia. The function of spleen is filtering the damaged red blood cells. Splenectomy is a contributory factor in aggregation of abnormal erythrocytes, platelet activation and release of procoagulant factors. Also due to splenectomy, many nucleated red blood cells appear in circulation. These blood cells can demonstrate adhesion molecules leading to intravascular thrombosis (6).

Also iron overload (serum ferritin more than 800 microgram/L or liver iron concentration more than 5 mg Fe/g dry weight) is a major contributory factor in developing pulmonary hypertension in thalassemia syndromes (9).

Aging, hemolysis, oxidative stress, prolonged inflammation, lower nitric oxide biological availability and abnormal regulation of arginine have been shown as other risk factors for PH in different published articles (10).

Teawtrakul et al., entered the clinical parameters remarkably associated with PH into a logistic regression model defined as E-SAAN scale. This risk score system consists of: 1. age > 35 years (2.5 points), 2. time after splenectomy > 5 years (2.5 points), and 3. β thalassemia /hemoglobin E (2 points). In this scale, the cutoff point ≥ 4.5 shows the high risk patients for PH in NTDT. With this cutoff, the sensitivity and specificity of the E-SAAN score turned out to be 94 and 71% respectively. However additional surveys are required to evaluate this scoring system in clinical practice (26).

Clinical manifestations

PH can manifest itself with many nonspecific clinical symptoms. Patients are often asymptomatic in early stages of the disease. Some PH symptoms including exertional dyspnea may be associated with chronic anemia accordingly delaying diagnosis of the disease in these patients.

Also respiratory symptoms of PH such as dyspnea and tachypnea can be detected during an attack of asthma (10). Weakness, fatigue, chest pain and syncope are considered as other non-specific symptoms (27). Rarely, lower extremity edema, reduction of oxygen saturation and *ascites* may be seen in advanced stages of PH in thalassemic patients (10).

Diagnostic methods

PH signifies a devastating condition such that delay in its diagnosis may be associated with a worsening outcome. An electrocardiogram should be routinely performed for all TM patients in order to detect prolonged QT interval corrected for pulse rate (QTc). In case the QT interval is prolonged, the risk of sudden death increases (28).

Echocardiography has routinely been used to detect PH among thalassemia patients. Doppler echocardiography can measure tricuspid regurgitation velocity (TRV), which is the pressure difference between the right ventricle and right atrium (29). TRV directly correlates with mean pulmonary artery pressure (PAP). Echocardiography is a screening technique to detect individuals being at an elevated risk for occurrence of PH; however, this method bears several limitations especially in high cardiac output conditions such as chronic hemolytic anemia (30). Janda et al. in a meta-analysis demonstrated the sensitivity and specificity of echocardiography for detection of PH as being 83 and 72% respectively (31). Pulmonary hypertension in general populations is defined as TRV≥2.9 m/sec but in sickle cell disease and other chronic hemolytic anemia like thalassemia, TRV greater than 2.5 m/sec represents PH. The best procedure for identification of PH is right heart catheterization (RHC). According to RHC, PH is described when mean pulmonary artery pressure (mPAP) exceeds 25 mmHg at rest (11).

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In figure 1, the echocardiographic picture of a TM case with severe PH has been shown.

One of the significant parameters measured in RHC is pulmonary wedge pressure (PWP) which differentiates pre- and post-capillary pulmonary hypertension; PWP≤15 mmHg signifies pre-capillary PH and PWP > 15 mmHg represents post-capillary PH (32). Typical example of pre-capillary PH is idiopathic subtype which is induced by obstruction of small lung arterioles. On the other hand, left cardiac disease (with preserved ejection fraction) can trigger post-capillary PH (33). Pre-capillary PH consists of clinical group 1 (pulmonary arterial hypertension), 3 (PH due to pulmonary disease and / or hypoxemia), 4 (chronic thromboembolic pulmonary hypertension) and 5 (PH with undefined mechanisms). Group 2 includes PH due to left heart disease (32).

Another technique for evaluation of exertional capacity is six-minute walk test. The baseline walk distance has an important value in PH. The distance walked in 6 minutes is markedly lower in patients with PH. Also in patients walking < 332 m, the life span appears to be much shorter. This test can be employed in monitoring the disease progression among thalassemic patients (34).

Other tests that can be used for assessment of PH in thalassemia syndromes consists of the parameters of abnormal function of right heart including NT-pro BNP and troponin level (6). NT-pro BNP >160 pg/ml indicates the risk of pulmonary hypertension being much higher. Moreover, LDH > 200 times is in favor of PH (11).

Cardiac MRI T2* is another non-invasive technique for assessment of myocardial iron overload. As ferritin level cannot predict the iron stores of myocardium (36-40), the advent of MRI T2* has substantially revolutionized management of thalassemic patients (35). It is often recommended that in every thalassemic patient on regular transfusion, cardiac MRI T2* be performed from age 10 and in patients with high ferritin levels from age 7 (41).

Myocardial iron overload often results in left ventricular dysfunction in TDT. Liver iron concentration (LIC) is the best method for assessment of total body iron in non-transfusion dependent thalassemic patients. MRI performed using either R2 or T2* methods is a non-invasive and precise technique for measurement of LIC. Increased LIC has been demonstrated to be correlated with pulmonary hypertension and thrombosis in NTDT (42). Musallam et al. have reported that in TI cases with LIC greater than 5 mg/g , the prevalence of vascular complications and other morbidities such as endocrinopathy or osteoporosis appears to be much higher than the patients with LIC<5mg/g (43). In several studies, authors have demonstrated a weak correlation between the heart and liver MRI T2*. Therefore, relying only on liver MRI T2* results for anticipation of the cardiac iron content is not a reliable method (44-46).

Treatment

The best treatment of PH in thalassemia is a therapeutic protocol which is directed at the underlying etiology. Major thalassemic patients at the early phase of pulmonary hypertension show a good response to shortening transfusion intervals. Regular transfusion therapy prevents chronic tissue hypoxia and also suppresses the release of pro-inflammatory cytokines. Furthermore, PH due to elevated pulmonary vascular resistance often responds to vasodilator drugs (41). Also aggressive chelation therapy prevents hemosiderosis and bears the potential to reduce the degree of PH (6). Taher et al. in a survey (OPTIMAL CARE) on 584 TI patients identified that hydroxyurea can increase the probability of hypogonadism but is preventive for PH (47).

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Hydroxyurea

Hydroxyurea boosts the level of Hb F via reactivation of γ genes. The efficacy of this drug in NTDT has been demonstrated in several published articles. Hydroxyurea can promote production of gamma chain and thus ameliorate imbalance of globin chains leading to neutralization of excess α chains. It also protects TI patients from PH by two mechanisms. The first is increased synthesis of Hb F which leads to improvement in tissue oxygenation and reduction of vasoconstriction so that the prevalence of PH diminishes. In the second mechanism, this drug bears the potential to reduce thrombocytosis and myeloid elements in the circulation following splenectomy (48).

L-Carnitine

L-Carnitine has a key role in oxidation of fatty acids and also normal mitochondrial function. In a study on β thalassemia major patients, El-Beshlawy et al. demonstrated that following administration of L-Carnitine (50 mg/kg/ day for a period of 3 months), a significant decline in pulmonary artery systolic pressure (PASP) is observed (49).

Sildenafil

Sildenafil is a strong blocker of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase-5 (PDE 5) resulting in relaxation of smooth muscles in lung vasculature. This drug has been deployed in both types of pulmonary hypertension, primary and secondary (50). Sildenafil causes a sustained and rapid reduction in tricuspid regurgitation in patients with PH. Also the long term consumption of this drug gives rise to progressive fall in pulmonary pressure without lowering systemic arterial blood pressure, and is well tolerated among thalassemic patients. Moreover, this drug appears to have a special effect on PH in sickle cell thalassemia patients (23).

Morris et al., in a 12-week open label survey on 10 cases with β thalassemia and TRV greater than 2.5 m/sec disclosed that administration of sildenafil can induce a marked decline in tricuspid regurgitation jet velocity. The authors then concluded that sildenafil bears the capacity to improve functional class as well as left ventricular and systolic/diastolic volume (51). Additionally, sildenafil is virtually effective in PH due to hypoxia (23).

Bosentan

Bosentan is an endothelin receptor analogue that is used for the treatment of PH. Bosentan therapy can improve thalassemia associated PH by alteration of hypercoagulable state. Patients who have a longer period of time after splenectomy are more vulnerable to PAH and show a lower response to this drug (52). Administration of bosentan can increase liver function tests and is not thus recommended in thalassemic cases affected with severe liver disease (6).

Tadalafil

This, like sildenafil, is a phosphodiesterase -5 inhibitor (PDE-5 I) and has been proved to have significant effects in reduction of pulmonary arterial systolic pressure (PASP) in individuals with idiopathic PH. In a study on TI patients, Jalalian et al. have projected the effect of this drug on PASP and TRV (53). In TI patients, due to endothelial dysfunction, production of NO which is a vasodilator and anti-proliferative factor slows down. Tadalafil augments NO level and exerts an influence on vasodilatation (51).

Epoprostenol

This drug is a synthetic prostacyclin. Prostacyclin attaches to its receptor on pulmonary artery smooth muscles and therefore heightens cyclic adenosine monophosphate (CAMP) leading to vasodilatation and platelet inhibition. Beside the vasodilatory effect, epoprostenol has anti-proliferative properties (54). The advantage of this drug in management of severe PH has been shown in many published studies but

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the most obvious limitation of all of these articles concerns their limited sample sizes (55-57). Ziesche et al., in a study on 7 cases with undefined severe PH showing a weak response to inhaled nitric oxide identified that continuous infusion of epoprostenol can ameliorate the pulmonary artery pressure (56). The first patient suffering from β thalassemia associated pulmonary hypertension, successfully treated with epoprostenol, was reported by Tam and Farber (55). Ussavarungsi and Burger presented a thalassemic case with severe pulmonary hypertension who had shown a dramatic response to epoprostenol therapy. Epoprostenol is the gold standard in severe or advanced PH resulting in reversal of symptoms, improvement in exercise capacity and increased survival (57).

Pulmonary Endarterectomy (PEA)

One of the devastating complications in thalassemic patients is chronic thromboembolic pulmonary hypertension (CTEPH) which occurs following pulmonary obstruction. In CTEPH, vascular occlusion and remodeling of pulmonary arteries may lead to a progressive and severe pulmonary hypertension. If promptly diagnosed and managed, CTEPH is not accompanied by an adverse outcome (58). In CTEPH, the organized thrombi attach to the medial layer of elastic pulmonary arteries and trigger complete obstruction or stenosis of the lumen of these arteries. Some therapeutic non-surgical options have been recommended for CTEPH including warfarin, bosentan, and riociguat (59). Riociguat is a new guanylate cyclase promoter which has documented benefits in the treatment of CTEPH. This drug can ameliorate exercise tolerance and vascular resistance of pulmonary system in these cases.

The sole therapeutic modality for CTEPH is known to be PEA. However, in individuals with occlusion of distal vessels or coexisting morbidities, this method proves not to be appropriate (60). This form of surgery must be carried out in expert centers with trained vascular surgeons and post-operative intensive care (61). The result of PEA on pulmonary vascular resistance and mean pulmonary artery pressure can be immediate and dramatic thus contributing to increased life span (62). In thalassemic patients with CTEPH who are inoperable, balloon pulmonary angioplasty (BPA) is another novel treatment modality, but additional investigations are necessary to establish the efficacy and benefits of BPA (63).

Summary of Findings

Cardiac disease is the main etiology of death in β-thalassemia and PH represents one of the most challenging morbidities in both forms of thalassemia, TDT and NTDT. Many factors have a contributory role in the pathogenesis of pulmonary hypertension in thalassemia. There are some disagreements about thalassemia-associated PH. One of the discrepancies concerns about the incidence of PH in TM and TI. Aessopos and Farmakis in a survey on 202 well treated thalassemia major patients illustrated that the main cardiac disease in thalassemia major is LV dysfunction with almost the absence of PH (22).

Also Vlahos et al. demonstrated that in major thalassemic patients, PH is relatively uncommon and often proves mild (21). However, Hagar et al. detected that 57% of thalassemia major patients with normal left ventricular systolic function show PH (64). These conflicts might have arisen from the discrepancies in the treatment of the participants in various studies performed in different countries.

In many cases, PH is a classic presentation of non-transfused thalassemia intermedia individuals and not a straightforward age-linked consequence due to the improved life span of these patients; however, in TM, regular transfusions can prevent hemolysis induced effects in pathophysiology of PH. Taher and

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colleagues have identified a remarkable association between age and prevalence of PH particularly after the age of 45 years (9).

Meloni and colleagues in a research on 60 thalassemia major cases reported that TRV has no correlation with age (29). In another study from Egypt, El Beshlawy et al. demonstrated 37.5% of children with thalassemia major showing PH (49). Their finding indicates that PH can develop even in young patients with thalassemia. This disparity concerning age can emanate from some key dissimilarities in the patient population and study plan. For example, in a research by Meloni et al. only five cases were older than 40 years.

In addition, time interval between the last transfusion and the time of echocardiography can affect TRV. Early post-transfusion echocardiography contributes to low prevalence of PH with marked elevation in TRV. A shorter interval may lead to suppression of ineffective erythropoiesis. Also increased transfusion intervals can elevate the rate of false positive cases of PH. On the other hand, late onset of transfusion is a documented parameter in developing PH (24).

The incidence of PH in TM and TI is different; in β TM patients, the rate of PH is between 2.1 and 79% whereas for TI it varies from 40 to50% (57). In most studies, echocardiography is used to report the rate of PH, which may lead to overestimation of the problem. However, by using RHC for confirmation of pulmonary hypertension in recent studies, the incidence of PH has been reported to be much lower (25). Additionally, the cutoff value for TRV varies considerably in different investigations. Using TRV≥2.5 m/sec to detect pulmonary hypertension in some recent trials, the prevalence of PH in TM varied between 10-20%. Moreover, regarding TRV ≥2.7 m/sec as the maximum normal limit may result in a much reduced rate of 1.6% (24).

Further, in a multicenter trial Derchi et al. disclosed that tricuspid regurgitation velocity greater than 3.2 m/sec can be a reliable indicator for PH and reported a prevalence of 1.6 in patients with β-thalassemia major (25). Because the cutoff value fails to be the same in different studies, the reported prevalence of pulmonary hypertension tends to differ. There are some conflicts about the effect of hemolysis in the pathogenesis of PH in TM. In most studies, the effect of hemolysis in occurrence of PH through nitric oxide - arginine mechanism has been shown. However, Meloni et al. reported no significant correlation between TRV and two main parameters of hemolysis; haptoglobin and LDH (29). In thalassemia major, the destruction of red blood cells occurs in the medulla (intramedullary hemolysis) and therefore the toxic RBC contents are not released into the circulation. Also Hagar and colleagues failed to demonstrate a difference around parameters of hemolysis among thalassemia major individuals with and without PH (64). Association between ferritin level and prevalence of PH is also challenging. Mokhtar et al. recognized that serum ferritin has a significant association with elevated TRV in patients with thalassemia major (65). Additionally, in a study performed in Egypt, the authors demonstrated a positive correlation between PH and serum ferritin. Furthermore, in this study a negative correlation was shown between PH and hemoglobin level (66). Musallam et al. also reported that increased liver iron concentration (LIC) can be a strong indicator for different morbidities including pulmonary hypertension in thalassemia intermedia (67).

In addition, Karimi and Derchi reported similar results (25,68). Taher and Cappellini in a recent study proved that serum ferritin >800 micgr/L or LIC> 5 mg Fe/g dry weight can be considered a risk

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factor for PH (9). These findings run counter to what Meloni identified. (29). In this study, no correlation was discerned between serum ferritin, hepatic iron or cardiac iron and TRV (29). Moreover, Hagar and the colleagues found no association between serum ferritin and PH (64).

The possible explanation regarding the absence of correlation between serum ferritin level and PH in Meloni's research may be due to the small number of cases with increased TRV, which is why the authors failed to demonstrate an association between ferritin and PH (29). Also in the research by Hagar et al., only 16 thalassemia major cases with PH and 12 cases lacking PH participated; the relationship between ferritin level and PH is missing in their study much likely due to limited number of the participants (64).

Conclusion

In recent years PH has become a known source of morbidity for thalassemic patients. The pathophysiology of PH in thalassemia is so sophisticated and complex, so a comprehensive evaluation regarding the etiology of PH appears to be necessary for treatment. Much as the pathophysiology of PH has well been described, there is no standard protocol for management of the abnormality. Majority of the research conducted on PH specific therapies including sildenafil, tadalafil, bosentan, L- Carnitine, riociguat, epoprostenol, endarterectomy and balloon pulmonary angioplasty have been set up as small case series. Moreover, these studies most often have a limited sample size and are virtually based on echocardiographic assessment of PH but not RHC which is seemingly the best procedure for diagnosis. Additional studies with greater sample sizes are recommended to evaluate the benefits and efficacy of such treatment modalities in order to establish more definitive guidelines regarding the thalassemia associated PH in future.

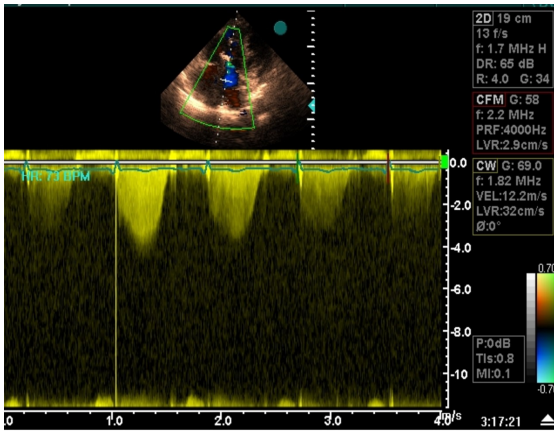

Figure 1: Tricuspid regurgitation maximum velocity method for measuring pulmonary artery systolic pressure.

Conflicts of interest

There are no conflicts of interest.

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