Evaluation of Tricuspid Regurgitant Jet Velocity in Thalassemia Patients with Splenectomy

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Abstract

**Background:** β-thalassemia is an inherited disorder of β-globin biosynthesis. Dysfunction in hemoglobin chain production, ineffective erythropoiesis, and hemolysis occur in β-thalassemia. Pulmonary arterial hypertension (PAH) is increasingly detected in patients with β-thalassemia, and splenectomy which decreases the need for blood transfusion increases the pulmonary artery pressure (PAP).

**Objectives:** This study aimed to assess the PAP in patients with β-thalassemia (male or female and major or intermedia) who had undergone splenectomy.

**Methods:** A total of 137 patients suffering from β-thalassemia were evaluated during the study. All subjects were referred for cardiac evaluation. Clinical history, presence of cardiac symptoms, and previous splenectomy were noted. Standard M-mode, 2D, and Doppler echocardiographic examinations were performed for all subjects. Patients with a tricuspid regurgitant jet velocity (TRV) ≥ 2.5 m/s were considered at risk for PAH.

**Results:** Average age of the patients was 21.15 ± 6.68 years. No significant difference was observed in the PAP between the 2 groups of thalassemia major and intermedia and also the 2 sex groups. Indeed, 6.6% of the patients had an increased PAP. The significant finding of the study was that the patients who had had splenectomy were significantly at an increased risk of PAH (P = 0.046).

**Conclusions:** The etiology of PAH in thalassemia is multifactorial such as inflammatory mediators. Also, the absence of the spleen plays an important role in developing a high TRV and PAH.

**Keywords:** Thalassemia, Splenectomy, Pulmonary Hypertension

1. Background

β-thalassemia is an inherited disorder. Production dysfunction in α- and β-globin hemoglobin chains is the cause of this abnormality. Therefore, the patients have ineffective erythropoiesis and hemolysis (1, 2) and they need to receive blood to prevent poor growth and bone deformities (3).

Iron overload is a common complication in thalassemia major that results in heart diseases and endocrine disorders (4). In patients with severe forms of β-thalassemia, including major and intermedia, iron overload and iron accumulation is seen in the reticuloendothelial system and in different tissues such as the liver, the endocrine system, and at a lower rate in the myocardium (5). Additionally, iron cardiac toxicity is a fundamental problem in these patients (6). In a large number of patients with thalassemia major, left ventricular (LV) systolic failure occurs with ventricular dilatation. Studies have shown that the function of the LV remains normal until the last stages of the disease (7). Iron-chelation drugs can reduce the toxicity of iron in some patients (5, 8). In spite of chelation therapy, there is still a risk of iron overload, organ failure, infection, oxidative stress, and chronic inflammations in patients with thalassemia (9). The cardiac involvement in patients suffering from thalassemia major is explained by 2 factors: increased cardiac output and iron depositions. In addition to these factors, left atrial dilation is clearly noticed compared to normal individuals. There is a relationship between diastolic changes and left atrial remodeling. In patients suffering from thalassemia, the pulmonary artery wedge pressure is more than that of normal individuals, which in many cases is associated with LV dysfunction.
Pulmonary arterial hypertension (PAH) is one of the reasons for patients’ death with hemolytic anemia. PAH is indicated with multifactorial signs such as interference between platelets, the coagulation system, erythrocytes, and endothelial cells with vascular and inflammatory mediators. The mechanisms which are involved include oxidative stress, thrombosis, splenectomy and iron overload.

2. Objectives

The present study sought to assess the pulmonary artery pressure (PAP) in patients with thalassemia (male or female and major or intermedia) who had undergone splenectomy.

3. Methods

The present research was conducted on patients with thalassemia major and intermedia admitted to Shahid Mohammadi Hospital, Hormozgan Province, Iran. This was a cross-sectional study performed on asymptomatic patients. Patients with diabetes mellitus and other endocrine diseases, including hypothyroidism, and also patients with significant valvular heart disease in echocardiography were excluded. The tests carried out included total iron-binding capacity (TIBC), iron, hematocrit, hemoglobin, white blood cells, and ferritin (Table 1). All the above-mentioned tests were carried out before administrating the cell pack.

Echocardiography was performed simultaneously by a cardiologist and an echocardiography fellow using a Vivid 3 machine in the parasternal 2- and 4-chamber views. Ventricular and atrial diameters were measured by M-mode study. Left ventricular ejection fraction (LVEF) was evaluated using the visual assessment and also through LV volume study. LVEF was estimated in general and an EF < 55% was considered as LV systolic dysfunction. Also, via Doppler mode and through appropriate criteria, LV diastolic properties such as early diastolic filling (E waves) and atrial contraction (A wave) were obtained. The E/A ratio and deceleration time (DT) were investigated (Table 1). LV diastolic and systolic diameters were calculated based on the body surface (end-diastolic dimension index) by the linear method and were compared to those of normal individuals. Diastolic function was evaluated according to the early diastolic filling velocity by mitral inflow Doppler study to mitral annulus tissue Doppler velocity ratio (E/e'). Early diastolic filling velocity by mitral inflow Doppler study to mitral annulus tissue Doppler velocity ratio; FEV, forced expiratory volume; FVC, forced vital capacity.

3.1. Statistical Analysis

All basic and echocardiographic parameters are shown as means ± SDs for the continuous and as counts (percentages) for the categorical variables. Some nominal data were compared between 2 subgroups of patients (according to TRV) using the $\chi^2$ test. A $P < 0.05$ was considered statistically significant. The statistical analyses were conducted using SPSS 16 for Windows (SPSS Inc., Chicago, Illinois).

4. Results

The study population comprised 137 patients: 51 (37.2%) male and 86 (62.2%) female patients. The age range of the participants was from 12 to 45 years, with the average age 2 groups of TRV $\geq 2.5$ m/s and TRV $< 2.5$ m/s. In all patients, spirometry was performed and forced vital capacity (FVC), forced expiratory volume (FEV), and FEV/FVC parameters were evaluated.
being 21.15 ± 6.68 years. Totally, 119 (86.9%) patients had thalassemia major and 18 (13%) had thalassemia intermedia. Fifty-two (33%) patients had E/e’ ≤ 8 and 85 (62%) had 8 < E/e’ < 15. In this study, no significant difference was observed in the PAP between the 2 groups of thalassemia major and intermedia (Table 2) and also between the 2 sex groups (Table 2).

Table 2. Evaluation of TRV in the Thalassemia Patients Based on Sex, Splenectomy, and Type of Thalassemia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TRV &lt; 2.5 m/s, (%)</th>
<th>TRV ≥ 2.5 m/s, (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>96.1</td>
<td>3.9</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Female</td>
<td>91.9</td>
<td>8.1</td>
<td></td>
</tr>
<tr>
<td>Splenectomy</td>
<td>86.5</td>
<td>13.5</td>
<td>0.046</td>
</tr>
<tr>
<td>No splenectomy</td>
<td>96</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Thalassemia major</td>
<td>93.3</td>
<td>6.7</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Thalassemia intermedia</td>
<td>94.4</td>
<td>5.6</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: TRV, tricuspid regurgitant jet velocity.

Nine (6.6%) patients had an increased PAP, and the significant finding of the study was that the patients who had had splenectomy were significantly at an increased risk of PAH (p = 0.046) (Table 2 and Figure 1). There were no significant differences in hemoglobin, hematocrit, ferritin, and TIBC between the patients with a normal PAP and those at risk of PAH. Additionally, the basic echocardiographic data and also spirometry data showed no significant differences in the findings of FVC, FEV1, and the FEV1/FVC ratio between the 2 groups of patients with a normal PAP and those at an increased risk of PAH.

5. Discussion

The results of the current study demonstrated that the thalassemia patients who had undergone splenectomy had a higher rate of PAH. However, contrary to the existing literature, our results showed no clear difference in the amount of PAH between the patients with thalassemia major and those with thalassemia intermedia. The main reason is the limited number of patients with thalassemia intermedia in our study.

Thalassemia is an important disease in the world, with a higher prevalence in the Middle East, Mediterranean, Asian subcontinent, and Southeast Asia. A significant number of thalassemia patients live in Iran, where the primary care program for thalassemia was commenced in 1997 with a view to reducing the disease’s complications (12). In thalassemia, increased iron absorption from the digestive system and iron overload via blood transfusion result in organ damage. One of the most important causes of death in these patients is dilated cardiomyopathy, followed by PAH and restrictive cardiomyopathy (13). The treatments for thalassemia major include red blood cell transfusion, chelation therapy, and splenectomy. Splenectomy can increase the risk of infection and thrombosis. Different studies have shown that while the risk of thrombosis is high in thalassemia patients subjected to splenectomy, the risk in patients with thalassemia intermedia is higher than that in those with thalassemia major (14).

PAH is a finding in patients with hemoglobinopathy, but its prevalence is different in patients with thalassemia. For example, one of the most common cardiovascular findings in patients with thalassemia intermedia, which accounts for about 20% to 25% of all β-thalassemia cases, is that the severity of PAH is higher in patients with thalassemia intermedia than in those with thalassemia major (15).

Patients with thalassemia who have undergone splenectomy have a particularly high risk of thrombotic events in the pulmonary vascular bed and an absolute risk of PAH. Overall, these patients are likely to develop portal hypertension. Therefore, directly or indirectly, splenectomy can cause PAH in these patients (16). Splenectomy plays an important role in adjusting iron load in patients with thalassemia (17). In patients with hemoglobinopathy, there are several reasons for hyper coagulation such as na-
tive erythrocyte procoagulation surface, genetic disorders of coagulation, endothelial dysfunction, splenectomy, and vasculopathy (15). The other mechanism for elevated pulmonary pressure in hemoglobinopathies is volume overload due to anemia, which increases the pulmonary blood flow and leads to the arteriopathy of the pulmonary vessels (18). A study conducted by Ammar et al. (19) showed that, after splenectomy, the risk of thrombosis and thromboembolic events increased in their patients with thalassemia major and that splenectomy led to increased microparticles in blood circulation and provided a foundation for venous thromboembolism.

Some studies have demonstrated that most of the thalassemia patients who receive a poor treatment undergo splenectomy. Poor treatment of thalassemia leads to low hemoglobin concentrations and more splenomegaly. Patients with regular blood transfusion and appropriate iron chelation have a low incidence of splenomegaly and are less likely to develop PAH (20). Indeed, the absence of a normal spleen function (asplenia) and hemolysis in patients with thalassemia are 2 important factors leading to an increase in TRV and PAP. Therefore, these patients experience a rise in their platelet count, platelet activity, and level of endothelin-1 (21).

5.1. Conclusions

In summary, we conclude that splenectomy is one of the important factors in the development of PAH in thalassemia patients regardless of age, gender, and type of thalassemia.

5.2. Study Limitations

The important limitation of the present study is that we did not perform right heart catheterization for a more precise assessment of the PAP.

References


