Clinical Indicators for Pulmonary Arterial Hypertension in Thalassemia

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Objective: *To explore clinical indicators for pulmonary arterial hypertension (PAH) in thalassemia (Thal).*
Material and Method: *A study was conducted in thalassemia patients at Chiang Rai Hospital, Chiang Rai, Thailand. Pulmonary artery systolic pressure (PASP) was determined by doppler echocardiography and PAH was defined as PASP > 35 mmHg. Patient characteristics were extracted from medical records. Characteristics of patients with and without PAH were compared. Risk indicators were explored with logistic regression analysis.*
Results: *Two hundred twenty four patients were included, 144 E/β-Thal, 37 homozygous β-Thal and 43 Hb H disease. There were 65 patients (29.0%) with PAH, 53 (81.5%) with E/β-Thal, 8 (12.3%) with homozygous β-Thal and 4 (6.2%) with Hb H disease. In a multivariable analysis, features significantly associated with PAH were E/β-Thal (OR = 1.98, 95% CI; 1.29-3.01) and post splenectomy status (OR = 2.36, 95% CI; 1.17-4.73).*
Conclusion: *Significant indicators for PAH in thalassemia were E/β-Thal and post splenectomy status.*

Keywords: *Thalassemia, Pulmonary Arterial hypertension, Splenectomy*

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Pulmonary arterial hypertension (PAH) has been reported as one of the common cardiac complications in b-thalassemia (β-Thal) patients[1,2]. Sonakul et al reported thrombi in small pulmonary arteries in 44% of splenectomized hemoglobin E/β thalassemia (E/β-Thal) under autopsy[3]. In Greece, 10% of PAH was reported in thalassemia major, and more than 50% in thalassemia intermedia[2]. Its prevalence in Thailand was 43%[4]. Contributing factors of PAH are increased cardiac output from chronic anemia, increased pulmonary capillary wedge pressure likely from LV diastolic dysfunction from chronic iron overload and increased pulmonary vascular resistance from thrombotic pulmonary arteriopathy[5,6]. Early detection and prevention of severe PAH are effective and viable ways to decrease morbidities and mortalities. Few studies identified predictive characteristics of high pulmonary artery systolic pressure in thalassemia patients. PAH could not be detected early by clinical examination or electrocardiography or chest radiograph. Right heart catheterization is invasive, costly and has limited use in only large cardiac centers. Doppler echocardiography (ECHO) is more sensitive and is a commonly used noninvasive tool to detect PAH[7-9]. The authors studied PAH in thalassemia using ECHO to estimate the prevalence of pulmonary artery systolic pressure and to explore important clinical indicators for PAH in these patients.

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Material and Method

Two hundred twenty four adult (≥ 15 years) patients with thalassemia disease, who were treated at the hematology outpatient clinic, Chiang Rai Hospital, were evaluated and followed between January 2005 and June 2010, were included in this study. All patients had the diagnosis of Hb H disease, homozygous-Thal and E/β-Thal established by Hemoglobin (Hb) analysis

utilizing high performance liquid chromatography (HPLC). None of the patients had clinical evidence of other secondary causes of PAH, including HIV infection, collagen vascular diseases and chronic obstructive airway diseases. Acquired heart disease associated with pulmonary venous hypertension; mitral valve disease, congenital heart disease and hyperthyroidism were also excluded. No patients used the following classification of drugs: antiplatelet, anticoagulants, calcium channel blockers or vasodilators. The functional class status was defined by the New York Heart Association (NYHA) Classification (Class I: patients with no limitation of activities; they suffer no symptoms from ordinary activities, Class II: patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion, Class III: patients with marked limitation of activity; they are comfortable only at rest, Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.). The investigation included history taking and clinical examination. Hematologic evaluation consisted of complete blood count, Hb analysis (HPLC), reticulocyte count, serum ferritin and creatinine level, liver function test, hepatitis profile, HIV screening and thyroid function test. Cardiac evaluation consisted of chest radiograph, electrocardiography (ECG) and ECHO. Pulmonary artery systolic pressure (PASP), estimated by ECHO, was performed on all patients. ECHO was done by the same cardiologist. The patients' history including type of thalassemia and splenectomy status were hidden during echocardiographic examinations. The present study protocol was approved by the institutional research ethics committee and was carried out in accordance with the Declaration of Helsinki.

Echocardiographic procedure

Complete two-dimensional, M mode and Doppler (pulsed wave, continuous wave and color) echocardiography was performed at rest with a (echo machine) using standard protocol following the American Society of Echocardiography guidelines. In a recruited patient, a tricuspid regurgitation jet was sought from all available mid-precordial and apical positions until a flow signal with the maximum spectral representation of the highest velocities could be obtained. Peak velocity was recorded from a holosystolic regurgitant jet. From the maximum velocity (V) of the regurgitant jet, the systolic pressure gradient (DP) between the right ventricle and right atrium was calculated by the modified Bernoulli equation ($DP = 4V^2$). Right atrial pressure was estimated by the response of the inferior vena cava diameter to inspiration. Right atrial pressure was assumed to be 5 mm Hg if the inferior vena cava completely collapsed with inspiration, 10 mmHg if the inferior vena cava diameter decreased more than 50% during inspiration, and 15 mmHg if it decreased less than 50%. If the inferior vena cavas diameter was larger than 2.5 cm and reduced by less than 50% during inspiration, right atrial pressure was assumed to be 20 mmHg. Adding the transtricuspid gradient to the mean right atrial pressure provided the right ventricular systolic pressure or peak systolic pulmonary arterial pressure in the absence of right ventricular outflow tract obstruction. Pulmonary hypertension was defined as a PASP greater than 35 mmHg[9]. In case absent of TR, the end diastolic pulmonic regurgitant (PR) velocity was calculated using the pressure gradient between the pulmonary artery and right ventricular end diastolic pressure. Pulmonary artery pressure = $4 (VPR)^2$ + right atrial pressure[10].

Statistical analysis

Descriptive statistics were used. Baseline characteristics were compared using the Chi-squared or Fisher's exact test for categorical variables, t-test or Mann-Whitney U-test or Wilcoxon ranksum test was used to compare the mean difference of continuous variables where appropriated. Univariable and multivariable logistic regression analysis were used to identify factors associated with PAH. This data was presented by frequency, percentage, mean, median, standard deviation (SD), inter-quartile range (IQR), Odds ratio, 95% confidence interval and p-value. A p-value of less than 0.05 was considered as statistically significant.

Results

Patient characteristics of 224 thalassemia patients are summarized in Table 1. 144 E/β-Thal, 37 homozygous β-Thal and 43 Hb H disease were evaluated. PAH was detected in 65 (29.02%) patients, 53 (81.54%) E/β-Thal, 8 (12.31%) homozygous β-Thal and 4 (6.15%) Hb H disease. The mean age was 35.37 $\pm$ 15.67 years. The mean PASP was 50.66 $\pm$ 13.53 mm Hg. All patients had normal left ventricular ejection fraction. The PAH group had a higher proportion than that of the non-PAH group for E/β-thal (53 (81.54) vs. 91 (57.23), p = 0.001), splenectomy (44 (67.69%) vs. 71 (44.65%), p = 0.002), the mean duration after splenectomy (19.75 $\pm$ 8.86 vs. 13.2 $\pm$ 6.38 years, p <

Table 1. Patient characteristics (n = 224)

Characteristics	PAH*, n (%)	Non-PAH, n (%)	p-value
Number of patients	65 (29.02)	159 (70.98)	-
Gender			0.471
Male	24 (36.92)	67 (42.14)	
Female	41 (63.08)	92 (57.86)	
Age (years)	35.37 ± 15.67	31.13 ± 15.76	0.069
Weight (kg)	43.32 ± 15.89	43.98 ± 9.16	0.694
Height (cm)	150.52 ± 8.21	153.21 ± 10.96	0.076
Type of thalassemia			0.001
Hb H disease	4 (6.15)	39 (24.53)	
Homozygous β-thal	8 (12.31)	29 (18.24)	
E/β-thal	53 (81.54)	91 (57.23)	
Splenectomy	44 (67.69)	71 (44.65)	0.002
Post splenectomy duration (years)	19.75 ± 8.86	13.2 ± 6.38	<0.001
Red cell transfusion (units/year) Median (IQR)	4 (11)	2 (8)	0.013
Endocrine complication	25 (38.46)	41 (25.79)	0.059
Functional class statusNYHA class			
I	8 (12.31)	58 (36.48)	
II	51 (78.46)	101 (63.52)	
III	6 (9.23)	0	<0.001
Clinical right heart failure**	9 (13.85)	0	<0.001
Systolic blood pressure (mmHg)	104.31 ± 13.45	106.99 ± 13.38	0.176
Diastolic blood pressure (mmHg)	62.28 ± 7.79	63.25 ± 9.12	0.454
Pulse rate (/min)	85.20 ± 10.84	86.66 ± 11.16	0.371
Oxygen saturation (%)	96.51 ± 2.02	97.85 ± 2.60	<0.001
Chest radiograph: suggestive of PAH***	43 (66.15)	10 (6.41)	<0.001
ECG suggestive of PAH****	33 (50.77)	3 (1.94)	<0.001
Hemoglobin (g/dl)	6.44 ± 1.36	6.84 ± 1.29	0.045
Corrected white blood cells (x 10^3/mL)	10.69 ± 5.41	10.92 ± 5.96	0.794
Platelets (x 10^3/mL)	393.92 ± 296.14	430.42 ± 296.93	0.259
Reticulocyte count (%)	7.46 ± 6.34	8.89 ± 6.86	0.298
Nucleated RBC/100 WBC, median (IQR)	28 (194)	11 (213)	0.334
Serum ferritin (mg/L)	3,759.54 ± 3267.67	2,307.66 ± 1886.46	<0.001
Indirect bilirubin (mg/dl)	2.0 ± 1.16	2.41 ± 1.94	0.063
HBsAg positive	2 (3.17)	9 (5.77)	0.426
Anti-HCV positive	8 (12.70)	18 (11.54)	0.810
Echocardiographic findings			
PASP (mmHg)	50.66 ± 13.53	26.05 ± 5.89	-
36-50 mmHg (mild)	40 (61.54)	-	
51-70 mmHg (moderate)	17 (26.15)	-	
> 70 mmHg (severe)	8 (12.31)	-	
LVEF (%)	62.17 ± 7.22	63.25 ± 7.02	0.301
LVESd (mm)	9.43 ± 2.05	9.06 ± 1.84	0.196
LVEDd (mm)	51.55 ± 6.42	50.08 ± 5.52	0.089
MPAd (mm)	26.61 ± 5.19	24.16 ± 3.33	0.005
RVd (mm)	28.55 ± 5.69	27.08 ± 4.34	0.084
Poor right ventricular systolic function	7 (10.77)	0	<0.001
Tricuspid regurgitation	61 (93.85)	32 (20.25)	<0.001
Diastolic function			
Mitral valve E:A ratio	1.38 ± 0.26	1.43 ± 0.51	0.913
Mitral valve DT (ms)	204.57 ± 52.98	220.60 ± 46.61	0.441

* Pulmonary arterial hypertension
** Elevated jugular venous pressure, hepatojugular reflux and edema
*** right interlobar pulmonary diameter of grater > 16 mm and Hilar to thoracic ratio > 0.44
**** right-axis deviation, R/S ratio > 1 in lead V1-3, R/S ratio < 1 in lead V5 or V6, right atrial enlargement
DT = deceleration time; LVEDd = left ventricular end diastolic diameter; LVEF = left ventricular ejection fraction; LVESd = left ventricular end systolic diameter; MPAd = main pulmonary artery diameter; RVd = right ventricular diameter

0.001), functional class status (Fc II 51 (78.46%) vs. 101 (63.52%) and Fc III 6 (9.23%) vs. 0, $p < 0.001$), clinical right heart failure (9 (13.85%) vs. 0), $p < 0.001$), oxygen saturation (96.5 ± 2.02 vs. $97.85 \pm 2.60\%$, $p < 0.001$). Patients with PAH received more blood transfusions during the preceding 12 months than those without PAH (4 (11) vs. 2 (8) units, $p = 0.013$). The PAH group had a lower the hemoglobin concentration than the non-PAH group (6.44 ± 1.36 vs. 6.84 ± 1.29 g/dl), $p = 0.045$) and they had higher serum ferritin levels ($3,759.54 \pm 3,267.67$ vs. $2,307.66 \pm 1,886.46$ mg/L, $p < 0.001$).

There were no statistically significant differences in gender, age, height, weight, endocrine complications, blood pressure, pulse rate, white blood cell count, platelet counts, percentage of nucleated red blood cells (nRBCs) to white blood cell count (WBC), reticulocyte count and indirect bilirubin level between PAH and non-PAH group. All had normal creatinine levels. None of the patients had clinical evidence of thromboembolism. In the PAH group, only 43 of 65 chest radiographs (66.15%) and 33 of 65 ECGs (50.77%) showed evidence of PAH.

Echocardiographic findings showed that patients with PAH had a significantly larger main pulmonary artery diameter, and a higher percentage of patients with poor right ventricular systolic function and tricuspid regurgitation (26.61 ± 5.19 vs. 24.16 ± 3.33 mm, $p = 0.005$, 7 (10.77) vs. 0, $p < 0.001$ and 61 (93.85) vs. 32 (20.25), $p < 0.001$, respectively).

Univariable and multivariable analysis are shown in Table 2 and 3. In a multivariable analysis, features significantly associated with PAH were E/β-Thal (OR 1.98 [1.29-3.01]) and post splenectomy status (OR 2.36 [1.17-4.73]).

Discussion

The prevalence of PAH reported in the patients was 29%. None of them had clinical evidence of acute or chronic deep vein thrombosis (DVT) (unilateral leg swelling, dilated superficial veins, chronic leg ulcer) which correlated with the findings of Sonakul et al which did not report emboli from DVT in autopsy[3]. Regular blood transfusions and iron chelation had been reported to prevent PAH in thalassemia major[11], but the authors did not find that the patients without

Table 2. Univariable association between clinical indicators and PAH

Indicators	Odds ratio	95% CI	p-value
Type of thalassemia			
Hb H disease or Homozygous β-thal	1	-	-
E/β-thal	3.30	1.60-6.79	<0.001
Splenectomy	2.59	1.39-4.84	0.002
Post-splenectomy duration ≥ 15 years	4.68	1.95-11.19	<0.001
Number of red cell transfusion > 6 units/year	1.92	1.04-3.52	0.033
Hemoglobin ≤ 6 g/dl	2.15	1.16-3.96	0.012
Serum ferritin > 1,000 μg/L	3.79	1.48-9.70	0.003

Table 3. Multivariable association between clinical indicators and PAH

Indicators	Adjusted odds ratio	95% CI	p-value
Type of thalassemia			
Hb H disease or Homozygous β-thal	1	-	-
E/β-thal	1.98	1.29-3.01	0.002
Splenectomy*	2.36	1.17-4.73	0.016
Number of red cell transfusion > 6 units/year	1.69	0.80-3.56	0.166
Hemoglobin ≤ 6 g/dl	1.15	0.56-2.36	0.695
Serum ferritin > 1,000 μg/L	2.45	0.92-6.54	0.073

* Splenectomy and post-splenectomy duration are collinearity

PAH received more blood transfusions than the patients with PAH because of the number of unit blood transfusions was calculated for only the preceding 12 months. This higher level of blood transfusions may imply more severe disease in patients with PAH. The previous study showed that high serum ferritin level was significantly associated with pulmonary hypertension[12]. The authors also found 2.45 times the chance to detect PAH in the patients with serum ferritin higher than 1,000 μg/L. However, the association was not statistically significant. In the present study the authors propose that the predictive factors for PAH in thalassemia include, E/β-Thal, post splenectomy status, number of red cell transfusion, hemoglobin and serum ferritin level, which were 72.15% accurate.

In the authors' study, features significantly associated with PAH were E/β-Thal and post splenectomy status. These findings are consistent with the proposed pathogenesis of other authors. The possible mechanisms leading to PAH after splenectomy may involve nucleated red blood cells, platelet activation and the coagulation cascade[5,6,13-17]. Moreover, thalassemic red blood cells can induce thrombotic complications. These cells have increased membrane expression of anionic phospholipids that accelerate thrombin generation and activate platelets[14]. The mechanisms are likely to be intensified in splenectomized patients with thalassemia, as they have more abnormal red blood cells and red blood cell precursors than their non-splenectomized counterparts. Pathophysiologic changes in post-splenectomy β-Thal leading to PAH are increased circulating PS (phosphatidylserine)-exposed RBCs which facilitate the coagulation process and activated platelets which cause vasculopathy and microthrombi leading to increased pulmonary vascular resistance index and vascular occlusion[5,6].

PAH can be associated with all kinds of chronic hemolytic anemia[14,18]. Therapeutic strategies of PAH are still controversial. Some authors suggested that the development of PAH could be prevented, by starting transfusion and chelation therapy early in life for patients with thalassemia intermedia[2].

Conclusion

PAH is the main feature of cardiac complications in β-Thal. The authors' findings indicate that the indicators for PAH are E/β-Thal and post splenectomy status. A serial ECHO to estimate PASP in high-risk groups for early appropriate treatment may be beneficial. Furthermore, the authors' studies evaluated the role of antiplatelets and regular blood transfusions in thalassaemia with PAH.

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Potential conflicts of interest

None.

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ลักษณะบ่งชี้ภาวะความดันในหลอดเลือดแดงปอดสูงในผู้ป่วยธาลัสซีเมีย

นลวันท์ เชื้อเมืองพาน, วัฒนา วงศ์เทพเตียน, วีระศักดิ์ นาวารวงศ์, อภิชาต สุคนธสรรพ์, สุภร จันท์จารุณี, ชไมพร ทวิชศรี, ชยันตร์ธร ปทุมานนท์

วัตถุประสงค์: *เพื่อศึกษาลักษณะบ่งชี้ภาวะความดันในหลอดเลือดแดงปอดสูงในผู้ป่วยธาลัสซีเมีย*
วัสดุและวิธีการ: *เป็นการศึกษาในผู้ป่วยธาลัสซีเมียที่โรงพยาบาลเชียงรายประชานุเคราะห์โดยใช้ Doppler echocardiography ในการวัดค่า pulmonary artery systolic pressure (PASP) โดย PASP > 35 mmHg ถือว่ามีภาวะความดันในหลอดเลือดแดงปอดสูง และวิเคราะห์เปรียบเทียบปัจจัยที่แตกต่างระหว่างกลุ่มที่มีและไม่มีภาวะดังกล่าว*
ผลการศึกษา: *ผู้ป่วย 224 ราย: E/β-Thal 144 ราย homozygous β-Thal 37 ราย และ Hb H disease 43 ราย พบภาวะความดันในหลอดเลือดแดงปอดสูงทั้งหมด 65 ราย (29.02%) เป็น E/β-Thal 53 ราย (81.54%) homozygous β-Thal 8 ราย (12.31%) Hb H disease 4 ราย (6.15%) จากการวิเคราะห์ถดถอยลอจิสติกพบลักษณะที่สัมพันธ์กับภาวะความดันในหลอดเลือดแดงปอดสูงคือโรค E/β-Thal (OR 1.98 [1.29-3.01]) และภาวะหลังตัดม้าม (OR 2.36 [1.17-4.73])*
สรุป: *ลักษณะบ่งชี้ภาวะความดันในหลอดเลือดแดงปอดสูงในผู้ป่วยธาลัสซีเมียคือ E/β-Thal และภาวะหลังตัดม้าม*