Original Article

Hemodynamic and Echocardiographic Alterations in Beta-Thalassemia Hemoglobin E Patients Receiving Regular Transfusion and Iron Chelation Therapy

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Objective: Beta-thalassemia hemoglobin E (beta-thal/HbE) is the commonest beta-thalassemia disease. Cardiovascular complications are still the leading cause of death in these patients. Regular transfusion with iron chelation has been currently more employed. Yet studies on hemodynamic and cardiovascular changes in this particular patients are still lacking. We aimed to define hemodynamic and cardiovascular characteristics in beta-thal/HbE patients receiving regular transfusion concomitant with iron chelation compared to healthy controls.

Materials and Methods: Cross-sectional study of 40 beta-thal/HbE patients receiving regular transfusion and iron chelation over one year and 40 age-sex-matched healthy controls was conducted. Hemodynamic and echocardiographic parameters were evaluated.

Results: The age (mean ± SD) of patients was 34±10 years. Beta-thal/HbE patients demonstrated significant differences in following parameters compared to healthy controls (all $p<0.001$): mean blood pressure (76.7±8.7 vs. 86.8±10.8 mmHg), stroke index (51.3±12.7 vs. 36.7±8.3 ml/m^2), cardiac output index (3.9±1.1 vs. 2.5±0.6 L/min), vascular resistance index (9.81±3.28 vs. 12.42±2.26 mm·min/L·m^2), systemic arterial compliance index (1.26±0.48 vs. 0.69±0.22ml/m^2/mmHg), left ventricular systolic and diastolic volume index (48.2±14.0 vs. 37.4±9.2 and19.1±5.7 vs. 13.2±4.2 ml/m^2). Biventricular systolic and left ventricular diastolic functions were well-preserved. Pulmonary arterial pressure was significantly elevated in beta-thal/HbE. However, the prevalence of pulmonary arterial hypertension (PAH) was 20% which was lower than previous populations receiving occasional transfusion.

Conclusion: Cardiovascular features compensating for longstanding anemia remain detectable in beta-thal/HbE patients receiving regular transfusion and iron chelation. Higher cardiac output, lower systemic vascular resistance and an enlarged left ventricular chamber were found in this particular population. However, systolic and diastolic functions remained well-preserved despite chronic transfusion.

Keywords: β-thalassemia/HbE, regular transfusion, echocardiography, hemodynamics

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Thalassemia syndromes are highly prevalent in Thailand. Approximately 30% - 40% of Thais carry thalassemic genes, while up to 1% of population suffers from thalassemia diseases. β-thalassemia/Hemoglobin E (β-thal/HbE) is the most common form of β-thalassemia disease and has become a major public health burden. Approximately 100,000 Thais suffer from β-thal/HbE with at least 3,000 affected newborns annually[1].

This disorder demonstrates marked clinical variability due to several modified genetic determinants. The majority of patients are classified as non-transfusion dependent thalassemia or thalassemia intermedia[2]. In past decades, patients with β-thal/HbE patients usually received occasional transfusion to ease their anemic symptoms and rarely received adequate parenteral iron chelation[3]. However, the current treatment of thalassemia diseases has been substantially improved due to greater understanding in their pathophysiological process, better blood transfusion policy, available oral iron chelating

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agents, and improvement in hematopoietic stem cell transplantation[4]. In addition, several large cohorts of β-thalassemia disease demonstrated that regular transfusion and iron chelation may be protective for pulmonary arterial hypertension (PAH), while splenectomy was a strong risk factor for PAH[5-8]. Therefore, more frequent or regular transfusions and adequate iron chelation have been widely adopted in current practice, which may modify natural history of disease including cardiovascular complications in this particular population. Until now, hemodynamic assessments of patients with β-thal/HbE receiving current treatment strategy have not been well-characterized. We aimed to assess hemodynamic and cardiovascular functions using echocardiography in β-thal/HbE patients who have received long-term regular transfusion and iron chelation compared with normal healthy population. In addition, we also compared cardiovascular characteristics between splenectomized and non-splenectomized β-thal/HbE patients.

Materials and Methods

Patients and study design

The cross-sectional study of adult β-thal/HbE patients, aged more than 18 years, compared with healthy controls were conducted from May to September 2015 at King Chulalongkorn Memorial Hospital. Age-sex matched healthy subjects with no underlying diseases and normal physical examination and laboratory results were enrolled from check-up clinic. Cardiovascular symptoms and signs were taken by cardiologists. Medical data were reviewed from medical records. All included β-thal/HbE patients met the following criteria: 1) regular transfusion defined as an average of packed red cell transfusion ≥1 unit monthly at least one year, 2) taking any iron chelating agent over one year and 3) no clinically decompensated cardiac failure. Regarding the institution policy, patients were regularly transfused to maintain pre-transfusion hemoglobin (Hb) of ≥7 g/dL. Subjects with significant structural or congenital heart diseases, cardiac arrhythmias, known risk factors of secondary PAH such as chronic lung diseases and chronic smoking, decompensated chronic liver diseases and pregnancy were excluded. Echocardiographic and hemodynamic data were measured in both groups. Laboratory results and amounts of blood transfusion were averaged from previous 12 months before the enrollment.

Informed consents were obtained from all participants. The study was approved by the Institutional Review Board of Faculty of Medicine, Chulalongkorn University and followed the Declaration of Helsinki.

Systemic arterial hemodynamic study

Systemic blood pressure was measured using automated arm-cuff sphygmomanometer in supine position after resting in quiet study rooms more than 10 minutes before the echocardiographic assessment. Pulse pressure (PP) was the difference between systolic blood pressure (SBP) and diastolic blood pressure (DBP). Mean arterial pressure (MAP) was calculated by DBP + PP/3. Systemic arterial compliance (SAC) was calculated from the ratio of SV to PP. Systemic vascular resistance (SVR) was estimated by MAP/CO. Several parameters such as SV, SVR and SAC were proportional to the body sizes, therefore, body surface area (BSA) was used to adjust these parameters as their indices.

Echocardiographic assessment

Echocardiographic evaluation was performed using ultrasound machine (IE33 or EPIQ 7C, Philips, Bothell, Seattle WA, USA) and a phase-array transducer by cardiologists and experienced sonographers. The protocol included standard 2-dimesional and color Doppler echocardiography in parasternal and apical views. The images were stored at the minimum of 3 consecutive cardiac cycles. Echocardiographic parameters were analyzed using Xcelera software version 3.2. Cardiac function parameters of left ventricular systolic and diastolic functions, right ventricular systolic functions, pulmonary artery pressure and stroke volume (SV) were measured and calculated according to guideline of the American Society of Echocardiography[9]. Left ventricular ejection fraction (LVEF) was derived from biplane method. Cardiac output (CO) was calculated as SV multiply by heart rate (HR) at the time of measurements.

Statistical analysis

Testing for the normality of the data was performed using Shapiro-Wilk test. Demographic data were presented as mean (± standard deviation, SD). Comparisons of continuous data and categorical data were analyzed by unpaired student t-test and Chi-square method, respectively. Correlations between variables were determined by Pearson correlation coefficient. A p-value<0.05 was considered statistically significant. All statistic parameters were computed using SPSS

version 16.0 for Window (Chicago, SPSS Inc.)

Results

From May to September 2015, there were each 40 subjects enrolled in the β-thal/HbE group and in the age- and sex-matched healthy control group. The demographic, clinical and basic laboratory profiles of the thalassemia and the control groups were summarized in Table 1. The mean (±SD) age of the thalassemia patients was 34.1 (±9.9) years, whereas the mean age of the controls was 36.4 (±8.8) (p = 0.30). Males (50%) and females (50%) were equal in both groups.

Patients with β-thal/HbE had significantly smaller body builds compared to controls. Among 40 β-thal/HbE, there were 28 (70%) splenectomized patients. All patients have received chronic transfusion and iron chelation. An average of packed red cell transfusion was 18.9 (±11.2) units per year. The majority (82.5%) of patients received oral iron chelating agents. Deferiprone (70%) was the most iron chelating drugs prescribed followed by deferoxamine (17.5%) and deferasirox (12.5%).

Hematological profiles showed that β-thal/HbE patients had severe anemia and strikingly high serum ferritin, which might explain significantly higher fasting plasma glucose and increased liver enzymes compared to those of the controls. However, there were no patients diagnosed as diabetes or clinically documented cirrhosis.

Hemodynamic and echocardiographic assessments demonstrated that β-thal/HbE patients had remarkable hemodynamic and cardiac functions different from healthy controls. Hemodynamic profiles and echocardiographic features of the thalassemia and the control groups were summarized in Table 2 and Table 3, respectively.

Patients with β-thal/HbE had significantly lower SBP ($p < 0.001$), DBP ($p = 0.004$) and MAP ($p < 0.001$) compared to those of controls, but had significantly faster HR ($p<0.001$). In addition, hemodynamic profiles derived from echocardiographic parameters demonstrated that thalassemia patients had increased SV, CO and SAC (all $p<0.001$), while a reduction in SVR ($p <0.001$). These hemodynamic parameters remained significantly different after adjustment with BSA.

The echocardiographic assessment indicated high volume load and enlarged both left atrial and ventricular chambers in the thalassemia group. Notably, LVEF and mitral E/A ratio as well as mitral E/e´ ratio between the thalassemia and the control groups were not significantly different, indicating preserved left ventricular systolic as well as diastolic functions in β-thal/HbE patients.

The right-sided parameters including tricuspid annular plane systolic excursion (TAPSE) and pulse tissue Doppler S wave (S´) demonstrated preserved right ventricular systolic function. Furthermore, the β-thal/HbE group had significantly higher pulmonary arterial systolic pressure (PASP) and mean pulmonary arterial pressure (mPAP) but no significant increase in pulmonary arterial diastolic pressure (PADP). Among 40 patients, there were 8 (20%) and 8 (20%) of patients with mPAP ≥25 mmHg or PASP ≥35 mmHg, respectively. All patients with mPAP ≥25 mmHg were splenectomized (8 of 28; 28.6%), while 6 of 8 with PASP ≥ 35 mmHg were splenectomized (6 of 28; 21.4%). Of 8 with mPAP ≥25 mmHg, all were classified as mild PAH (mPAP of 25 to 40 mmHg).

Subgroup analysis demonstrated that splenectomized patients had significantly increased white blood counts and platelet counts compared to those of non-splenectomized patients. However, there were no significant differences of other demographic, laboratory, hemodynamic and echocardiographic profiles between two groups, (Table 4).

Discussion

Cardiovascular disorders are a leading fatal complication in β-thal/HbE patients. Chronic transfusion without adequate iron chelation leads to left-sided cardiac failure. In contrast, less frequent transfusion, especially in splenectomized patients, results in development of PAH and subsequent right-sided cardiac failure[5-8]. In the past, many physicians avoided transfusion in β-thal/HbE patients as most patients were usually well-compensated and able to survive into adulthood without chronic transfusion. In addition, insufficient blood components and a lack of oral iron chelating agents further limited regular transfusion in this patient group. With current knowledge and better treatment availability, regular transfusion concomitant with iron chelation has been more employed in current clinical practice. In the present study, we evaluated hemodynamic and echocardiographic parameters of β-thal/HbE patients who received current treatment strategy with regular transfusion and iron chelation.

Compared to age- and sex-matched healthy controls, we found that β-thal/HbE patients had significantly lower SBP, DBP and MAP. This

Table 1 Baseline characteristics of β-thalassemia/Hb E patients and normal healthy controls

	β-thalassemia/Hb E patients (n = 40)	Healthy controls (n = 40)	p-value
Patient characteristics			
Age (years)	34.1±9.9	36.4±8.8	0.28
Gender (male)	20	20	
Height (cm)	158.5±8.9	164.9±9.1	0.003*
Weight (kg)	50.4±9.8	65.2±15.0	<0.001*
Body surface area (m^2)	1.48±0.16	1.72 ± 0.21	<0.001*
PRBC transfusion (unit/year)	19.6±10.6	0	N/A
Laboratory data			
Hemoglobin (g/dL)	7.8±1.1	13.6±1.3	<0.001*
Hematocrit (%)	25.3±3.7	41.4±3.7	<0.001*
MCV (fL)	73.0±6.1	80.8±14.7	0.004*
RDW (%)	23.2±3.1	13.6±1.0	<0.001*
Platelet (/µL)	439,000±302,822	269,000±76,315	0.006*
WBC (/µL)	31,400±28,070	7,676±2,122	<0.001*
corrected WBC (/µL)	11,700±5,707	0	N/A
Nucleated RBC (/µL)	243.4±260.2	0	N/A
Neutrophil (%)	48.1±12.9	59.4±10.3	<0.001*
Lymphocyte (%)	39.8±14.3	29.7±8.8	0.002*
Monocyte (%)	5.9±3.6	5.0±1.8	0.16
Fasting blood sugar (mg/dL)	106.2±32.2	88.6±7.7	0.003*
BUN (mg/dL)	12.7±3.9	11.5±2.8	0.18
Creatinine (mg/dL)	0.47±0.16	0.82 ±0.14	<0.001*
eGFR (ml/min/1.73m^2)	183±55	103±17	<0.001*
AST (U/L)	46.4±32.0	22.7±8.2	<0.001*
ALT (U/L)	42.1±24.4	25.7±16.0	0.003*
Ferritin (ng/ml)	3,490 ±3600	152 ±132	<0.001*

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, eGFR = estimated glomerular filtration rate, MCV = mean corpuscular volume, PRBC = packed red blood cell, RDW = red cell distribution width, WBC = white blood cell, N/A = not applicable
* Significant at $p<0.05$

Table 2. Hemodynamics data of β-thalassemia/Hb E patients and normal healthy controls

Hemodynamics data	β-thalassemia/Hb E patients (n = 40)	Healthy controls (n = 40)	p-value
Systolic blood pressure (mmHg)	105.6±12.8	123.6±15.9	<0.001*
Diastolic blood pressure (mmHg)	62.3±8.2	68.4±9.3	0.004*
Mean arterial pressure (mmHg)	76.7±8.7	86.8±10.8	<0.001*
Pulse pressure (mmHg)	43.3 ± 10.3	55.2±10.5	<0.001*
Heart rate (beats/minute)	75.2±8.2	67.7±8.0	<0.001*
Stroke volume (mL)	75.3±19.6	62.6±12.3	0.001*
Stroke index (mL/m^2)	51.3±12.69	36.7±8.3	<0.001*
Cardiac output (L/min)	5.7±1.6	4.2±0.9	<0.001*
Cardiac index (L/min/m^2)	3.9±1.1	2.5±0.6	<0.001*
SAC (ml/mmHg)	1.85±0.69	1.16±0.28	<0.001*
SAC index (ml/m^2/mmHg)	1.26±0.48	0.69±0.22	<0.001*
Estimated SVR (mm·min/L)	14.56±4.39	21.28±4.30	<0.001*
Estimated SVR index (mm·min/L·m^2)	9.81±3.28	12.42±2.26	<0.001*

SAC = systemic arterial compliance, SVR = systemic vascular resistance
* Significant at $p<0.05$

Table 3. Echocardiographic parameters of β-thalassemia/Hb E patients and normal healthy controls

Echocardiographic data	β-thalassemia/Hb E patients (n = 40)	Healthy controls (n = 40)	p-value
LVEDD (mm)	50.4±6.2	46.3±3.7	0.001*
LVESD (mm)	28.4±6.4	27.1±3.3	0.27
LVEDD index (mm/m^2)	34.2±4.1	26.4±5.3	<0.001*
LVESD index (mm/m^2)	19.2±4.2	15.4±3.3	<0.001*
LVEDV (mL)	70.2±23.0	65.0±19.8	0.31
LVESV (mL)	27.9±9.2	22.9±8.5	0.021*
LVEDV index (mL/m^2)	48.2±14.0	37.4±9.2	<0.001*
LVESV index (mL/m^2)	19.1±5.7	13.2±4.2	<0.001*
LVEF biplane (%)	72.44±7.6	71.9±5.8	0.72
LVMI (g/m^2)	98.0±22.7	83.7±19.40	0.005*
Mitral E velocity	109.0±19.0	77.9±15.5	<0.001*
Mitral A velocity (cm/s)	73.3±16.0	57.9±13.8	<0.001*
Mitral E/A ratio	1.6±0.5	1.4±0.4	0.07
Medial e' velocity (cm/s)	9.9±2.3	9.3±2.0	0.24
DT (msec)	187.3±28.1	180.5±22.8	0.25
Mitral E/e' ratio	11.1±3.0	10.6±12.4	0.83
TAPSE (cm)	28.3±5.8	24.7±3.4	<0.001*
S' (cm/s)	14.1±2.8	14.2±9.7	0.94
LAVI (ml/m^2)	26.8±7.7	17.4±3.8	<0.001*
PASP (mmHg)	29.2±15.3	19.3±7.4	<0.001*
PADP (mmHg)	10.8±4.1	9.4±3.5	0.095
mPAP (mmHg)	17.0±6.6	12.7±4.3	0.001*

DT = deceleration time, LAVI = left atrial volume index, LVEDD = left ventricular end-diastolic diameter, LVEDV = left ventricular end-diastolic volume, LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic diameter, LVESV = left ventricular end-systolic volume, LVMI = left ventricular mas index, mPAP = mean pulmonary artery pressure, PADP = pulmonary artery diastolic pressure, PASP = pulmonary artery systolic pressure, S' = pulse tissue Doppler S wave, TAPSE = tricuspid annular plane systolic excursion

* Significant at $p<0.05$

observation was similar to the previous study in young thalassemia major patients[10]. Despite their increased HR, SV and CO, decreased systemic blood pressure in β-thal/HbE patients was due to significant increase in SAC and subsequent reduction in SVR. The previous study demonstrated a significantly decrease in plasma norepinephrine levels in thalassemia major patients which might partially explain lower SVR in the thalassemia group[10]. Our study found that cardiac index (r = -0.684, $p<0.001$), SAC index (r = -0.626, $p<0.001$), and SVR index (r = 0.745, $p<0.001$) were strongly correlated with Hb levels. Therefore, lower systemic vascular tone is possibly to compensate for anemia and high flow states to increase tissue perfusion.

The distinct hemodynamic parameters, which were remarkably different from normal values, in β-thal/HbE patients are clinically significant, especially in critical care management. Patients with thalassemia diseases, especially after splenectomy, are at risk for severe infections and septic shock. Hemodynamic managements are usually guided by these parameters. Although invasive monitoring is a standard of care, echocardiographic assessment is a non-invasive test commonly employed in critical care units. Hemodynamic resuscitation using general normal values may mislead fluid and vasopressor therapy in thalassemia patients.

Echocardiographic features including LVEDD index, LVESD index, LVEDV index and LVESV index demonstrated enlarged cardiac chambers and high volume load. All parameters were significantly correlated with Hb levels; LVEDD index (r = -0.689, $p<0.001$), LVESD index (r = -0.379, $p = 0.003$), LVEDV index (r = -0.416, $p = 0.001$), and LVESV index (r = -0.559, $p<0.001$). Therefore, high cardiac output state, volume load and cardiac enlargement are consequently compensatory mechanisms for longstanding anemia in β-thal/HbE patients.

Notably, β-thal/HbE patients who have received chronic transfusion and iron chelation had preserved left ventricular systolic and diastolic functions despite

Table 4. Comparison of baseline characteristics, hemodynamic and echocardiographic data between splenctomized and non-splenectomized β-thalassemia/Hb E patients

	Splenectomy (n = 28)	No splenectomy (n = 12)	p-value
Patient characteristics			
Age (years)	33.29±10.0	35.9±9.6	0.45
Gender (male)	13	7	
Height (cm)	157.1±9.4	162.3±6.8	0.12
Weight (kg)	50.3±10.6	50.8±7.6	0.89
Body surface area (m^2)	1.48±0.18	1.50±0.10	0.67
PRBC transfusion (unit/year)	17.8±6.8	23.8±16.0	0.098
Laboratory data			
Hemoglobin (g/dL)	7.9±1.0	7.4±1.3	0.21
Hematocrit (%)	25.8±3.3	24.3±4.6	0.24
MCV (fL)	75.3±4.3	67.9±6.6	0.003*
RDW (%)	22.4±2.9	24.9±2.8	0.023*
Platelet (/μL)	568,000±270,514	149,000±106,875	<0.001*
WBC (/μL)	39,500±28,277	5,139±931	0.005*
corrected WBC (/μL)	13100±5304	5139±931	<0.001*
Nucleated RBC (/μL)	290.4±263.3	20.3±11.6	<0.001*
Neutrophil (%)	47.8±14.7	49.0±6.4	0.72
Lymphocyte (%)	38.5±16.0	43.5±7.3	0.35
Monocyte (%)	6.5±3.9	4.6±2.4	0.16
Fasting blood sugar (mg/dL)	108.7±34.9	99.4±23.7	0.45
BUN (mg/dL)	12.7±3.8	12.6±4.4	0.94
Creatinine (mg/dL)	0.45±0.17	0.54 ±0.12	0.15
eGFR (ml/min/1.73m^2)	192±58	155±36	0.09
AST (U/L)	49.5±35.6	37.8±17.7	0.33
ALT (U/L)	43.2±22.5	39.2±30.0	0.67
Ferritin (ng/ml)	3,840 ±4000	2,682±2372	0.36
Hemodynamic data			
Systolic blood pressure (mmHg)	104.8±13.7	108.3±9.3	0.51
Diastolic blood pressure (mmHg)	62.3±8.6	62.6±6.9	0.90
Mean arterial pressure (mmHg)	76.4±9.4	77.9±11.1	0.67
Pulse pressure (mmHg)	42.6±10.2	45.62±10.5	0.47
Heart rate (beats/minute)	75.8±7.4	73.5±10.5	0.46
Stroke volume (mL)	76.2±19.8	73.3±19.8	0.67
Stroke index (mL/m^2)	51.8±12.6	50.2±14.2	0.75
Cardiac output (L/min)	5.9±1.8	5.2±1.1	0.18
Cardiac index (L/min/m^2)	4.0±1.1	3.6±0.8	0.23
SAC (ml/mmHg)	1.93±0.77	1.60±0.27	0.08
SAC index (ml/m^2/mmHg)	1.33±0.52	1.05±0.21	0.04*
Estimated SVR (mm·min/L)	14.37±4.83	15.28±2.75	0.62
Estimated SVR index (mm·min/L·m^2)	9.75±3.64	9.99±2.0	0.82
Echocardiographic data			
LVEDD (mm)	50.4±6.1	50.5±6.6	0.99
LVESD (mm)	28.4±4.5	28.6±9.7	0.94
LVEDD index (mm/m^2)	34.1±4.1	34.7±4.5	0.7
LVESD index (mm/m^2)	19.2±2.8	19.3±7.1	0.97
LVEDV (mL)	74.5±21.6	65.2±19.2	0.31
LVESV (mL)	28.2±8.7	30.6±8.9	0.61
LVEDV index (mL/m^2)	50.5±12.8	43.5±13.8	0.3
LVESV index (mL/m^2)	19.3±5.7	20.9±5.2	0.52
LVEF biplane (%)	74.6±6.1	67.4±8.6	0.24
LVMI (g/m^2)	97.1±23.4	100.9±21.7	0.66
Mitral E velocity	108.9±18.6	109.3±20.8	0.95
Mitral A velocity (cm/s)	71.4±16.2	77.7±15.1	0.28
Mitral E/A ratio	1.7±0.6	1.4±0.3	0.23
Medial e' velocity (cm/s)	9.7±2.4	10.3±2.1	0.44
DT (msec)	186.5±28.3	189.1±28.8	0.8
Mitral E/e' ratio	11.1±3.3	11.2±2.1	0.92
TAPSE (cm)	47.7±7.4	30.6±7.2	0.45
S' (cm/s)	13.4±2.8	14.9±4.0	0.2
LAVI (mL/m^2)	27.2±7.3	25.7±9.2	0.63
PASP (mmHg)	28.6±17.1	30.6±10.6	0.72
PADP (mmHg)	11.0±4.5	10.5±2.8	0.74
mPAP (mmHg)	16.9±7.6	17.2±3.8	0.39

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, DT = deceleration time, eGFR = estimated glomerular filtration rate, LAVI = left atrial volume index, LVEDD = left ventricular end-diastolic diameter, LVEDV = left ventricular end-diastolic volume, LVEF = left ventricular ejection fraction, LVESD = left ventricular end-systolic diameter, LVESV = left ventricular end-systolic volume, LVMI = left ventricular mas index, MCV = mean corpuscular volume, mPAP = mean pulmonary artery pressure, PADP = pulmonary artery diastolic pressure, PASP = pulmonary artery systolic pressure, PRBC = packed red blood cell, RDW = red cell distribution width, S' = pulse tissue Doppler S wave, SAC = systemic arterial compliance, SVR = systemic vascular resistance, TAPSE = tricuspid annular plane systolic excursion, WBC = white blood cell

* Significant at $p<0.05$

chronic transfusion and remarkably high serum ferritin levels. Previous studies demonstrated significantly higher left ventricular abnormalities in β-thalassemia major compared to β-thalassemia intermedia[7, 11]. In addition, pulse wave tissue Doppler imaging parameters demonstrated development of diastolic dysfunctions in patients with normal systolic functions in both pediatric and adult β-thalassemia major[12, 13]. However, our study was unable to demonstrate any statistical differences between the β-thal/HbE and the control groups. All patients in our study have received iron chelation, mostly deferiprone, which can more preferentially and effectively remove cardiac iron compared to deferoxamine and deferasirox despite stable serum ferritin levels[14,15]. Therefore, iron chelating therapy, in particular deferiprone, may prevent and/or delay development of cardiac hemochromatosis. The longer longitudinal follow up is required to determine the burden of cardiac complications of the current treatment strategy.

Our study demonstrated significantly increased PASP and mPAP in thalassemia patients. PAH is a distinct cardiovascular complication of β-thalassemia intermedia including β-thal/HbE[5-8]. Regular lifelong transfusion in β-thalassemia major results in left ventricular dysfunction leading to cardiac failure, which may develop since early life. Although less frequent transfusion therapy in thalassemia intermedia including β-thal/HbE preserves left ventricular systolic function but promotes development of PAH. The pathogenesis of PAH is complicated and remains poorly understood[16,17]. Splenectomy is the strongest risk factor for development of PAH in β-thalassemia intermedia, while blood transfusion and iron chelation are protective factors[6, 18-20]. Surprisingly, our study population, for which 70% splenectomized patients accounted, did not find any different hemodynamic and echocardiographic parameters, including PASP and mPAP between splenectomized and non-splenectomized patients. The prevalence of PAH defined as either mPAP ≥25 mmHg or PASP ≥35 mmHg in our regularly transfused β-thal/HbE patients (20%) was lower than those of previous reports defined as PASP ≥35, ranging from 36.8% - 45.0%[18-20]. All patients were asymptomatic and classified as mild pulmonary hypertension defined as mPAP of between 25 and 40 mmHg. In addition, the prevalence of PAH using PASP ≥ 35 mmHg in our splenectomized population (21.4%) was also substantially lower than in previous studies, ranging from 52.5-72.7%[18-20]. Notably, most β-thal/HbE patients in previous studies did not receive regular transfusion policy. The previous case reports demonstrated significantly decreased pulmonary arterial pressure after chronic transfusion as well as a decrease in several activated coagulation and inflammation markers[21,22]. Furthermore, the recent prospective study in β-thal/HbE patients with PAH demonstrated a greater reduction in PASP and a better improvement in the 6-minute walk distance in patients receiving chronic transfusion over one year compared to those receiving occasional transfusion[23]. Interestingly, the previous study demonstrated the effectiveness of deferiprone therapy in the significant reductions of mPAP and pulmonary vascular resistance among β-thal/HbE patients receiving intermittent transfusion[24]. Therefore, regular transfusion with adequate iron chelation may be beneficial to prevent cardiovascular complications, especially PAH, in β-thal/HbE disease.

Conclusion

The present study characterized hemodynamic and echocardiographic alterations in β-thal/HbE patients receiving regular transfusion and iron chelation. Decreased systemic blood pressure and SVR were distinct characteristic hemodynamic changes. High output state and volume load due to longstanding anemia have impacted enlarged cardiac chambers, while preserved biventricular systolic and left ventricular diastolic functions. There were no statistical differences in any hemodynamic and echocardiographic parameters between splenectomized and non-splenectomized patients.

What is already known on this topic?

Cardiovascular abnormalities are common findings found in β-thal/HbE patients. Enlarged cardiac chambers with preserved left ventricular systolic functions are compensatory mechanisms for chronic anemia. PAH is a common complication in intermittently transfused patients, especially in a splenectomized subgroup

What is this study adds?

The β-thal/HbE patients have distinct cardiovascular parameters. Regular transfusion concomitant with iron chelation therapy does not impair both systolic and diastolic functions. Although pulmonary arterial pressure remains elevated, the prevalence of PAH even in the splenectomized population in our study is much lower than previous reports which most patients received occasional

transfusion, thus suggesting protective effects of regular transfusion and iron chelation on development of PAH in β-thal/HbE patients.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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