Systolic and Diastolic Myocardial Function, Comparative Study between Splenectomized and Non Splenectomized Thalassemic Patients

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Abstract: Cardiac complications still the most common causes of death in patients with major B thalassemia. Iron overload causes severe and permanent cardiac damage even more than untreated anemia . **Aim of the work:** The aim of this study was to compare splenectomized and non splenectomized B thalassemic patients echo cardio graphically as regard systolic and diastolic myocardial function. Forty B thalassemic patients whom regularly visit both pediatric and internal medicine hematology clinic and 20 ae and sex matched volunteers controls were recruited in the study . The age range of patients was (2-18)years. Patients were classified into two groups: group I (non splenectomized) including 20 patients whom were medically treated with frequent blood transfusion plus chelation therapy and the other splenectomized group(group II) including 20 patient receive the same treatment and had done surgical splenectomy more than six months. **Results:** There was significant difference between the two studied groups regarding fractional shortening (p= 0.006) , mitral E/A ratio (p =0.03), Tei index (p = 0.001), pulmonary artery pressure (p =0.001) while no significant difference between the two groups regarding ejection fraction (p = 0.197). In non splenectomized B thalassemic patients, there was significant positive correlation between amount of blood transfusion/year and ejection fraction (p =0.03, r =0.46) while in splenectomized B thalassemic patients, there was significant positive correlation between Hb level and fractional shortening (p =0.01, r = 0.56) and between Hb level and ejection fraction (p =0.005,r =0.59) also, there was significant positive correlation between serum ferritin and mitral E/A ratio (p =0.04, r =46). **Conclusions:** Diastolic function of right and left heart in B thalassemic patients is affected by multiple transfusions and final iron overload. While splenctomy partially improve systolic and diastolic myocardial performance, pulmonary hypertension may be a consequence of splenectomy in B thalassemic patients.

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1. Introduction

Inherited hemoglobin disorders are amongest the most common single gene defects in human**(1)** and thalassemias are the commonest of this group**(2).** Beta thalassemia major (TM) represents a group of recessively. inherited hemoglobin disorders**(3)** where beta globin chains synthesis are decreased resulting in an excess of alpha chains. This leads to increased synthesis of the hemoglobin without beta chains [e.g. Hb-F (alpha2 gamma2), Hb-A2 (alpha2delta2)] and free alpha chains form tetramers (alpha4), which are very insoluble and precipitate in red cells leading to increased fragility and early red cell death**.(1)** The estimated prevalence of beta thalassemia is 16% in Cyprus, 3-14% in Thailand and 3-8% in India, Pakistan, Bangladesh and China. Prevalence is low in African blacks (0.9%) and northern Europe (0.1%)**(4).** Cardiac complications in thalassemic patients are multiple and attributed to chronic anemia, infrequent transfusions and inadequate chelation therapy **(5).** A recent study shows that presence of certain major histocompatibility antigens/alleles may protect (HLA-DRB1*1401), while others may predispose (HLA-DRB1*0501) to the development of congestive cardiac failure. Therefore, genetic, immune and infective processes may also be important in the causation of heart disease in beta thalassemia major **(6).** Heart complications represent the leading cause of mortality in both forms of the disease. **(7)** Cardiac involvement in TM is generally characterized by iron-induced ventricular dysfunction, leading to heart failure.**(8-10)** However, the gradual adoption of what is currently considered to be the standard therapy by the different patient populations and the highly variable compliance of patients with this therapy have led to conflicting data with respect to the frequency of left ventricular (LV) dysfunction and the development of pulmonary hypertension. **(9-12)** At the same time, the cardiac benefits of a lifetime compliance with the standard therapy are not yet clear.**(13).**

Cardiac complications are still the most common cause of death in patients with major thalassemia. Iron overload causes severe and permanent cardiac damage even more than untreated anemia. Cardiac complications due to iron overload are recurrent pericarditis, recurrent forms of heart block, ectopic ventricular beats, ventricular tachycardia, ventricular fibrillation, cardiomegaly, left ventricular (LV) dysfunction and finally heart failure resistant to any therapeutic measures **(7).**

Impaired LV contractility was defined by an ejection fraction < 55% or a shortening fraction < 30%. **(14)**.

In thalassemic patients with normal systolic function and iron overload, the first sign of diastolic dysfunction is abnormality in LV relaxation time manifested as prolonged isovolumic relaxation time (IRT) **(15, 16).**

Myocardial performance index (MPI) or Tei index is a Doppler derived index of ventricular function that is free of geometric constraints. It involves simultaneous (or near simultaneous at equivalent heart rates) measurement of atrio-ventricular inflow and ipsilateral semi lunar outflow Doppler velocities. It allows to assess global function and because it incorporates both systolic and diastolic components of the cardiac cycle, it is also global from a temporal perspective as well. **(17)**.

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (PAP) of 25 mmHg or greater at rest or of 30 mmHg or greater during exercise and can result from a wide range of conditions. (18)

In thalassemia erythrocytes likely contribute to clot formation, particularly in splenectomized patients. Subsequent to splenectomy, abnormal erythrocytes are not filtered out; they remain in the circulation and trigger platelet activation and thrombosis, which then affect pulmonary circulation. Abnormal phospholipids exposure in the outer leaflet of red blood cells was reported in thalassemia patients, resulting in distorted red blood cell membrane that triggers thrombosis. **(19,20)** In addition, platelet-red blood cell interactions via adenosine diphosphate release and adherence of erythrocytes to endothelial cells can cause changes in the microvasculature. **(**21**)** Endothelial cell dysfunction was shown in PH of various etiologies, including in patients with sickle cell anemia and thalassemia, suggesting presence of inflammation, enhanced thrombosis, and arterial stiffness**.(**22**,**23**,**24**).**

Aim of the work:

The aim of this study was to assess and compare both systolic and diastolic myocardial function between non splenectomized and splenectomized B thalassemic patients.

2. Patients and Methods:

This studied was carried out in January to July 2011. Forty thalassemic patients whom regularly visit the pediatric and internal medicine hematology clinic in Menia university hospital and 20 apparently healthy age and sex matched volunteers as control group recruited in the study . The age range of patients was (2-18) years. Patients were classified into two groups: group I (non splenectomized) group including 20 patients were medically treated with frequent blood transfusion plus chelation therapy and the other splenectomized group(group II) including 20 patient receive the same treatment and have done surgical splenectomy.

Inclusion criteria:

Known B thalassemic patients regularly visiting and frequent closely followed up.

Exclusion criteria :

- Symptoms or signs of congestive heart failure at the time of echo-doppler exam., other clinical condition that affect myocardium as diabetes mellitus, chronic renal failure or hyper or hypothyroidism.
- History or proved congenital heart disease.
- History of cardio tropic drug intake till the time of examination.
- History of recent or chronic infection or inflammation.

All studied groups subjected to thorough history taking, clinical examination and Lab investigation including: Complete blood picture, Hb electrophoresis, serum iron and total iron binding capacity, serum ferritin. Radiological investigation including chest x ray and echo-doppler study. In echocardiography, all images were taken in left lateral position Myocardial systolic waves(S) and diastolic waves Eann and A ann expressed in Cm/sec, Mitral inflow velocity at the tip of mitral leaflets E and A (cm/sec), ejection fraction ,fractional shortening, Tei index and Pulmonary artery pressure were calculated to both studied patients and controls.

Statistical analysis:

All data are statistically analyzed using SPSS version 13. All numerical data are expressed as mean± SD. A two-sample Student's t test was used to assess the differences in the means between patients in both studied groups. Differences were considered to be statistically significant when p value ≤ 0.05.

3. Results:

Table (1): comparison between the two studied groups as regard some clinical and laboratory data.

Parameter	Group I	Group II	*P* value
Age(year)	2.625+1.3	10.15+3.3	0.001**
Hb (gm/dl)	8.05+0.77	10.625+0.7	0.001**
Transfusion(ml/kg/yr)	274.25+50.5	165.6+45.6	0.001**
Serum ferritin(ng/ml)	1357.5+488.9	832.9+134.3	0.001**
Fractional shortening (%)	37.95+4.3	34.5+3.4	0.006*
Ejection fraction (%)	274.2515.2	61.6+3.9	0.197
Mitral valve E/A ratio	1.62+0.3	1.815+0.18	0.03*
Tei index	0.349+0.077	0.612+0.1	0.001**
Pulmonary artery pressure(mmhg)	17.95+3.3	29.7+5.8	0.001**

* *P* value is significant if < 0.05 , E/A : ratio of peak flow velocity in early diastole to peak flow velocity in late diastole.

Table(2): Correlation between some laboratory and Echo cardiographic findings.

Parameter	Group	Fractional shortening	Ejection fraction	Mitral E/A ratio	Tei index	Pulm artery pressure(mmhg)
Hb (gm/dl)	GroupI	P=0. 11 r=-0.37	P=0.29 r=-0.25	P=0.83 r=-0.1	P=0.45 r=-0.18	P=0.89 r=-0.09
	Group II	P=0.01* r=0.56	P=0.005* r=0.59	P=0.67 r=-0.1	P=0.19 r=0.31	P=0.72 r=0.07
Transfusion /year	Group I	P=0.35 r=0.22	P=0.03* r=0.5	P=0.6 r=0.13	P=0.63 r=0.11	P=0.1 r=0.38
	Group II	P=0.87 r=0.04	P=0.87 r=0.38	P=0.82 r=0.06	P=0.29 r=-0.25	P=0.009* r=0.57
Serum ferritin (ng/ml)	GroupI	P=0.11 r=0.37	P=0.06 r=0.4	P=0.07 r=0.4	P=0.73 r=-0.08	P=0.24 r=0.28
	Group II	P=0.51 r=0.16	P=0.95 r=0.02	P=0.04* r=0.46	P=0.48 r=0.17	P=0.77 r=0.07

* *P* value is significant if < 0.05.

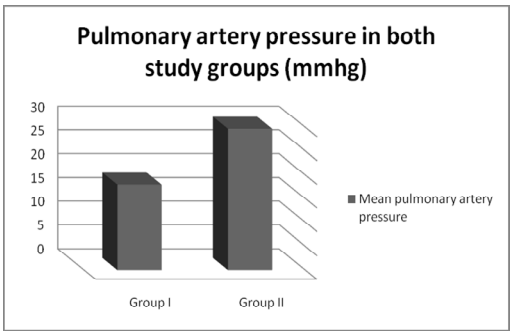

Figure (1): Comparison between the two studied groups as regard pulmonary artery pressure.

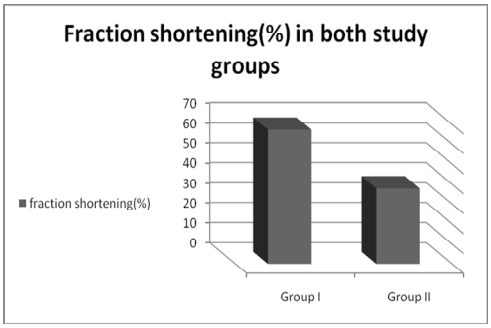

Figure (2): Comparison between the two studied groups as regard fractional shortening

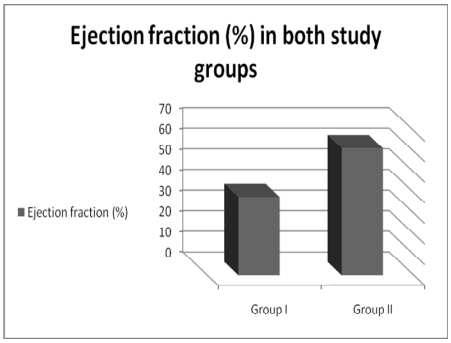

Figure (3): Comparison between the two studied groups as regard ejection fraction

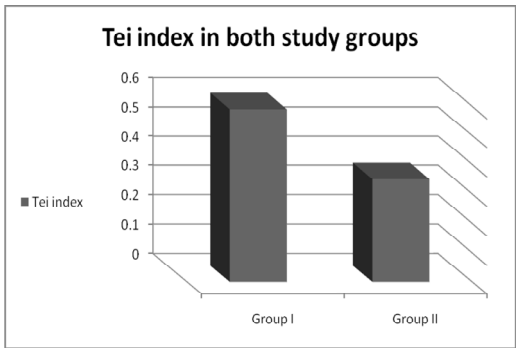

Figure (4): Comparison between the two studied groups as regard Tei index.

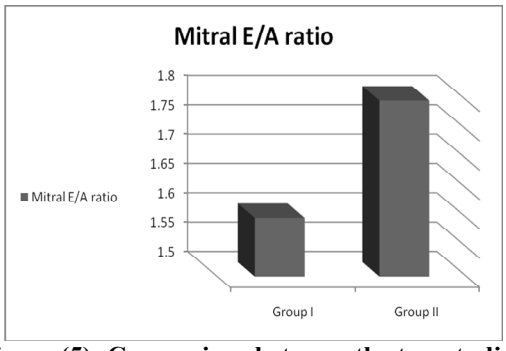

Figure (5): Comparison between the two studied groups as regard mitral E/A ratio.

4. Discussion

Cardiac complications represent the main cause of mortality in B thalassemia. **(7)**

Two main factors induce these cardiac complications: iron overload and high output state. The former is mostly due to multiple transfusions and, to a less extent due to chronic hemolysis and increase intestinal iron absorption, while the latter is a compensatory reaction to chronic anemia. In B thalassemia major , iron overload is considered the main cause of myocardial injury. **(25)**

This comparative study aimed to assess the myocardial function in non splenectomized transfusion dependant thalassemic patients and another group of

splenectomized thalassemic patients. As regard some lab Data, there was significant difference between the two studied groups as regard age (mean age in group I was 2.6+1.3 years while in group II , it was 10.2+3.2 years. This may be explained by the fact that surgical splenectomy in thalassemic patients usually done after the age of five. **(26)** Mean Hb level was significantly higher in group II than group I and the frequency of blood transfusion/year significantly decreased after splencetomy supporting the opinion that RBCs become resistant to hemolysis after splenectomy. **(27)**Also, removal of the spleen improve the hemoglobin level and subsequently, reduce the transfusion needs and the total blood volume**.(28,29)**

Significant difference between two groups as regard serum ferritin (higher in group I) suggesting that splenectomy improve hemoglobin concentration ,reduce transfusion needs and subsequently decrease the frequency of hemolysis while another opinion proved that serum ferritin is higher after splenectomy as splenectomy is associated with increase iron deposition and increase transferrin iron saturation. The further increase in the iron overload after splenectomy should be born into consideration before removal of this organ**.(30)** Assessment of myocardial function included assessment of systolic (by detection of ejection fraction and fractional shortening) and diastolic (by assaying mitral E/A ratio) myocardial function as well as myocardial performance(by detection of Tei index). There was significant difference between two groups as regard fractional shortening (increased in group I) while no significant difference between two groups as regard ejection fraction and in both groups are significantly lower compared with controls. Impaired LV contractility was defined by ejection fraction less than 55% or fractional shortening less than 30%. **(14)**

The cause of systolic dysfunction owed to decrease in left ventricular systolic performance due to both increase in the after load and a reduced contractile state secondary to iron toxicity **(31)**

The insignificant difference between both study groups as regard ejection fraction could be explained that iron overload appears to mediate impaired diastolic function, with the development of pulmonary hypertension leading to stiffness of myocardial wall. So it seems in the present study that patient's myocardial affection passed through impaired relaxation before the development of systole dysfunction **(32)**

A significant higher mitral E/A ratio in group I than Group II suggesting restrictive diastolic pattern and thus stiff left ventricular wall. **(33)**

Multi-transfused thalassemic children are more liable to left ventricular diastolic dysfunction suggested by impaired relaxation probably due to iron overload and anemia while in splenectomized thalassemic patients the left ventricular performance is better preserved with adjustment of serum ferritin less than 1000ng/ml. **(34)**

Significant difference between the two studied groups regarding Tei (higher in group I) index which is the index of ventricular dysfunction increased Tie index reflecting myocardial dysfunction this difference between two groups explained by increased after load in non slpenectomized transfusion dependant thalassemic patients owing to anemia and hypoxia as well as iron overload with sub sequent myocardial hemosidrosis. All these causes are decreased after splenectomy with consequent decrease in blood transfusion needs and increase of hemoglobin levels. Tei index is normalized or near normalized after splenectomy and continuity of iron chelation therapy.
Our splenectomized patients had significantly higher systolic pulmonary artery pressure than non splenectomized patient .

We have also studied other factors that can influence pulmonary artery pressure in our patients. Regular blood transfusion and iron chelation had been reported to prevent pulmonary hypertension in thalassemia major and to lower the incidence of splenectomy. **(35,36)** Although most of the reported patients with thalassemia with pulmonary hypertension were splenectomized**(13,37,38),** and to a lesser extent non splenectomized patients can also have pulmonary hypertension whereas some of them have normal pulmonary arterial pressure. The previous study showed that b-Thalassemia patients had a high proportion of PHT. This finding was consistent with a recent report, which also found that 50% of patients with B thalassemia intermediate with normal left ventricular ejection fraction had significant PHT. **(13)**
Splenectomized B thalassemic patients are at high risk of having impaired diastolic left ventricular function and pulmonary hypertension **(39)** Also, most forms of chronic hemolytic anemia, may develop pulmonary hypertension, suggesting that there is a syndrome of hemolysis-associated pulmonary hypertension. **(40)**
The importance of chronic hemolysis on the development of pulmonary hypertension through its negative effect on nitric oxide.**(41)**

Red cell membrane elements produced by hemolysis-induced oxidative damage have been discussed as a responsible mechanism for the elastic tissue injury. Degenerative elastic tissue lesions have been encountered in pulmonary autopsies in sickle-cell disease and may also be related to the development of pulmonary hypertension in hemoglobinopathies. **(42)**
The stress induced alteration of the left ventricular systolic performance showed a correlation with the total amount of blood transfused/year in non splenectomized B thalassemia. Even in patients with few blood units transfusion. An abnormal response of

left ventricular ejection fraction to exercise was found. **(43)**

In splenectomized thalassemic patients, a significant positive correlation was found between the amount of blood transfusion/year and pulmonary artery pressure. Regular blood transfusions and iron chelation had been reported to prevent PHT in thalassemia. **(35)** Also, in splenectomized thalassemic patients, mitral E/A ratio which reflect the left ventricular diastolic function was correlated significantly with serum ferritin. Cardiovascular prognosis in thalassemic patients if serum ferritin is maintained below 2500ng/ml is considered safe. Iron toxicity plays an important role in diastolic dysfunction and reduced myocardial performance. Cardiac hemosidrosis is one of the most important factors involved in the pathogenesis of B thalassemic cardiomyopathy. **(44)**

5. Conclusions:

Diastolic function of right and left heart in thalassemic patients is affected by multiple transfusions and final iron overload. Myocardial performance index of right and left heart is increased in these patients that show cardiac systolic and diastolic dysfunction. While splenectomy partially improve systolic and diastolic myocardial performance, pulmonary hypertension may be a risky consequence of splenectomy in B thalassemic patients.

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