ABSTRACT

**Background:** Chronic administration of large quantities of blood and inappropriate increase in iron absorption from the gastrointestinal tract inevitably lead to severe hemosiderosis in the whole body organs with impaired functions. Cardiac disorders related to biventricular failure are the most frequent cause of death in patients with beta-thalassemia major. Pulmonary complications in the form of restrictive and obstructive lung disease due to pulmonary hemosiderosis, recurrent heart failure.

**Objective:** to assess cardiac and pulmonary functions in patients with beta thalassemia major.

**Patients & methods:** This prospective study was conducted on 25 known β-thalassemia major children, 14 males and 11 females, their age ranged from 5.4 years to 15 years. They were selected from the pediatric clinic of Benha University Hospital. The study also included 25 apparently healthy children as a control group with matched age and sex during the period from March 2003 to January 2004.

All patients were subjected to thorough history taking, full clinical examination, ECG, echocardiography, and pulmonary function tests.

**Results:** The mean LVEDD (left ventricular end diastolic dimension) among cases was (4.728 ± 0.592) which was significantly higher than among controls (4.0 ±0.504) (p<0.05). The mean LVESD (left ventricular end systolic dimension) among cases was (3.076 ±0.58) which was significantly higher than among controls (2.464 ± 0.429) (P < 0.01). The mean LVM (left ventricular mass) among cases (123.68 ±13.034) was significantly higher than among controls (97.44 ±10.52) and this difference was highly significant (P < 0.001). The tricuspid E/A ratio was reversed in 5 (20%) of patients indicating right ventricular diastolic dysfunction. The ECG results revealed voltage criteria consistent with the diagnosis of left ventricular hypertrophy in 11 patients (44%), two patients (8%) showed right ventricular hypertrophy, one patient (4%) showed left
atria dilatation, and none of patients showed right atria dilatation. The mean FVC (forced vital capacity) among cases was (81.68 ± 11.025) and among controls (87.52 ± 3.584) and this difference was statistically significant (P<0.05). The mean FEV1/FVC (forced expiratory volume in first second / forced vital capacity) among cases (93.68 ± 6.447) was significantly higher than the control group (90.36 ± 1.868) (P < 0.05).

Conclusions: we conclude that patients with B-thalassemia major have abnormal left and right dimensions as well as relaxation abnormalities which may be a reflection of early myocardial damage. This early damage is detectable by a widely applicable echocardiography. Also the present study has shown that restrictive disease and reduced lung diffusing capacity are the predominant abnormalities of pulmonary function due to lung fibrosis.

INTRODUCTION

Thalassemia is the most common type of chronic hemolytic anemia in Mediterranean countries. It consists of several genetically determined disorders due to unequal synthesis of globin amino acids chains that cause ineffective erythropoiesis, hemolysis and anemia. The patients survival depends on repeated blood transfusions. Chronic administration of large quantities of blood and inappropriate increase in iron absorption from the gastrointestinal tract inevitably lead to severe hemosiderosis in the whole body organs with impaired functions (1).

Cardiac disorders related to biventricular failure are the most frequent cause of death in patients with beta-thalassemia major. Initial cardiac changes have been documented by conventional echocardiography before clinical; ECG or radiological manifestations became apparent (2).
Pulmonary complications in the form of restrictive and obstructive lung disease due to pulmonary hemosiderosis, recurrent heart failure, pulmonary vascular congestion, microthrombosis and impaired alveolar growth are of great interest because of their effect on the patient’s life expectancy and quality of life \(^{(3),(4),(5)}\).

**AIM OF THE WORK**

The aim of this work is to assess cardiac and pulmonary functions in patients with beta thalassemia major using echocardiography, pulmonary function tests and electrocardiogram.

**PATIENTS AND METHODS**

This study was conducted on 25 well known \(\beta\)-thalassemia major children, 14 males and 11 females, their age ranged from 5.4 to 15 years. They were selected randomly from the pediatric clinic of Benha University Hospital during the period from March 2003 to January 2004. The study also included 25 apparently healthy children as a control group with matched age and sex.

**All cases and control children were subjected to the following:**

1. Full medical history: with special emphasis on history of blood transfusion, desferoxamine therapy, and cardiac and chest symptoms.
2. Clinical examination: including general examination and local inspection, palpation, percussion and auscultation, of heart and chest.
3. Chest x-ray was done to all patients.
4. ECG: using Fukuda M-E, 500 AX.
5. Echocardiography: using ATL5000, echocardiography
examination included 2 dimensional, color flow mapping, Doppler display and M-mode modalities. The LVEDD, LVESD, LVM, FS, EF, pulmonary acceleration time, and tricuspid E/A ratio were measured.

6- Pulmonary function testing; FVC and FEV1/ FVC were measured.

Blood transfusion was given to all patients when hemoglobin (Hb) reached or decreased below 10 gm/dl. Every patient received 10-15 ml/kg packed red cells. The frequency of transfusion depended on Hb level and was nearly the same in all patients, (every 3-4 weeks).

9 patients did not receive desferoxamine and 16 patients received it irregularly after blood transfusion by subcutaneous infusion. That is why all our patients are poorly transfused and irregularly chelated.

**RESULTS**

Table (1) shows that the mean LVEDD, among cases was $4.728 \pm 0.592$ and among controls was $4.0 \pm 0.504$, and this statistically difference was significant ($P < 0.05$). The mean LVESD among cases was $3.076 \pm 0.58$ and among controls $2.464 \pm 0.429$ and the difference between cases and controls was highly significant ($P < 0.01$). The mean LVM among cases was $123.68 \pm 13.034$ and among controls was $97.44 \pm 10.52$ and this difference was highly significant ($P < 0.001$).

Also the mean FS and EF among cases was $31.84 \pm 5.713$ and $61.88 \pm 4.784$ respectively and among controls was $29.4 \pm 2.661$ and $60.24 \pm 2.223$ and this difference was statistically non significant ($P > 0.05$). The mean pulmonary acceleration time among cases was $112.76 \pm 11.727$ and among
controls was 121.6 ± 4.301 and the difference was significant (P< 0.05).

Table (2) shows that the tricuspid E/A ratio was reversed in 5 (20%) of patients indicating right ventricular diastolic dysfunction.

Table (3) the ECG results that revealed voltage criteria consistent with the diagnosis of left ventricular hypertrophy in 11 patients (44%), two patients (8%) showed right ventricular hypertrophy, one patient (4%) showed left atria dilatation, and none of patients showed right atria dilatation.

Table (4) shows the mean FVC among cases was 81.68 ± 11.025 and among controls 87.52 ± 3.584 and this difference was statistically significant (P<0.05). The mean FEV1/FVC among cases was 93.68 ± 6.447 and among control group was 90.36 ± 1.868 and this difference was statistically significant (P < 0.05).

**Table (1):** Mean LVEDD, LVESD, LVM, FS, EF, and pulmonary acceleration time among cases and controls.

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th></th>
<th></th>
<th>controls</th>
<th></th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \bar{X} )</td>
<td>Range</td>
<td>SD</td>
<td>( \bar{X} )</td>
<td>Range</td>
<td>SD</td>
<td></td>
</tr>
<tr>
<td>LVEDD In cm</td>
<td>4.728</td>
<td>3.7-5.7</td>
<td>±0.592</td>
<td>4</td>
<td>3.3-4.9</td>
<td>±0.504</td>
<td>4.482</td>
</tr>
<tr>
<td>LVESD In cm</td>
<td>3.076</td>
<td>2-4.1</td>
<td>±0.58</td>
<td>2.464</td>
<td>1.2-3.1</td>
<td>±0.429</td>
<td>4.242</td>
</tr>
<tr>
<td>LVM In grams</td>
<td>123.68</td>
<td>90-150</td>
<td>±13.034</td>
<td>97.44</td>
<td>80-144</td>
<td>±10.52</td>
<td>7.83</td>
</tr>
<tr>
<td>FS%</td>
<td>31.84</td>
<td>21-41</td>
<td>±5.713</td>
<td>29.4</td>
<td>24-35</td>
<td>±2.661</td>
<td>1.936</td>
</tr>
<tr>
<td>EF%</td>
<td>61.88</td>
<td>54-70</td>
<td>±4.784</td>
<td>60.24</td>
<td>55-65</td>
<td>±2.223</td>
<td>1.554</td>
</tr>
<tr>
<td>Pul. Acc. Time</td>
<td>112.76</td>
<td>80-123</td>
<td>±11.727</td>
<td>121.6</td>
<td>113-130</td>
<td>±4.301</td>
<td>3.539</td>
</tr>
</tbody>
</table>
Table (2): Distribution of the studied groups according to tricuspid E/A ratio.

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th></th>
<th>Controls</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>T</td>
<td>P value</td>
</tr>
<tr>
<td>Normal</td>
<td>20</td>
<td>80.0</td>
<td>25</td>
<td>100.0</td>
<td>236</td>
<td>&lt; 0.05 significant</td>
</tr>
<tr>
<td>Reversed</td>
<td>5</td>
<td>20.0</td>
<td>0</td>
<td>0.0</td>
<td>1.118</td>
<td>&gt; 0.05 not significant</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>100.0</td>
<td>25</td>
<td>100.0</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

Table (3): ECG results.

<table>
<thead>
<tr>
<th></th>
<th>LV hypertrophy</th>
<th>LA Dilatation</th>
<th>RV hypertrophy</th>
<th>RA Dilatation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases (n = 25)</td>
<td>11 (44%)</td>
<td>1 (4%)</td>
<td>2 (8%)</td>
<td>-</td>
</tr>
<tr>
<td>Controls (n= 25)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table (4): Mean FVC and FEV1/FVC among cases and controls.

<table>
<thead>
<tr>
<th></th>
<th>Cases (n = 25)</th>
<th>Controls (n = 25)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X</td>
<td>Range</td>
<td>SD</td>
<td>X</td>
<td>Range</td>
<td>SD</td>
<td>T</td>
</tr>
<tr>
<td>FVC</td>
<td>81.68</td>
<td>55-94</td>
<td>± 11.025</td>
<td>87.52</td>
<td>81-92</td>
<td>± 3.584</td>
<td>2.521</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>93.68</td>
<td>78-102</td>
<td>± 6.447</td>
<td>90.36</td>
<td>85-94</td>
<td>± 1.868</td>
<td>2.473</td>
</tr>
</tbody>
</table>

Fig (1) show pulsed wave Doppler on tricuspid valve there is RV diastolic dysfunction (Case No. 5)
DISCUSSION

Thalassemia is the most common type of chronic hemolytic anemia in Mediterranean countries and it is believed to be the most prevalent of all human genetic diseases. It’s inherited as an autosomal genetic disorder \(^{(6)}\).

Cardiac disorders related to biventricular failure are the most common cause of death in patients with beta-thalassemia major. Heart failure is caused by anemic hypoxia, cardiac hemosiderosis, arrhythmias and hyperdynamic circulatory overload \(^{(7)}\).

Beta-thalassemia major also affects pulmonary functions where restrictive pattern is the predominant abnormality in pulmonary function tests. A mild obstructive element can coexist with restrictive lung disease in a small number of patients \(^{(8)}\).

In this study both LVEDD and LVESD were significantly higher in patient than control group ( \(p < 0.05\)) and (\(P< 0.01\)) respectively. Cardiac dilatation occurs secondary to chronic anemia which means strong association between cardiac dilatation and chronic anemia. Our finding are similar to Khalifa et al \(^{(9)}\) who showed a significant increase of all cardiac dimensions by echocardiography (LAD- LVEDD-LVESD) more in regularly transfused patients. They stated that these cardiac structural changes are due to chronic anemia more than siderosis.

In the present study finding coincides with Walker \(^{(10)}\) and Kushner, et al \(^{(11)}\), they found that the mean LVM index was significantly increased in thalassemic patients versus controls \((P < 0.05)\), while in the present study there was highly significant increased LVM among cases versus controls \((P<0.001)\).
As regard the FS and EF there was no significant difference between patient and control group (P > 0.05). These results are similar to other reports which also demonstrated preserved left ventricular systolic function inspite of cardiac dilatation \(^{(2),(3)}\).

*Khalifa et al.*\(^{(9)}\) and *Desideri et al.*\(^{(12)}\) found insignificant difference between all the studied cases and controls as regards the mean values of EF and FS (P>0.05).

In this study the mean pulmonary acceleration time was significantly decreased in patient than control group (P<0.05). This finding coincides with a study done by *Hahalis et al.*\(^{(13)}\), they showed that the pulmonary hypertension in thalassemic patients results from pulmonary hemosiderosis.

In this study and study done by *Gharzuddine et al.*\(^{(14)}\), the right ventricular tricuspid dysfunction was observed in thalassemic patients more than control group.

The ECG results revealed voltage criteria consistent with the diagnosis of left ventricular hypertrophy in 11 patients (44%) , two patients (8%) showed right ventricular hypertrophy , one patient (4%) showed left atria dilatation, and none of patients showed right atria dilatation. *Khalifa et al.*\(^{(9)}\) found voltage criteria fulfilling left ventricular hypertrophy in (33%) of patients, voltage criteria of right ventricular hypertrophy in (15%) of patients and deep Q in V5 or V6 indicating septal hypertrophy in (7%) of patients.

A significant decrease in FVC was found in the patient's group compared to the control group (P<0.05). This indicates that the patient's group have restrictive pattern of pulmonary function
(mild to moderate restriction). Also FEV1/FVC was significantly higher in patient group than in the control (P<0.05). This indicates a mild degree of obstructive pattern of pulmonary function in β-thalassemia major patients. Analysis of these values indicated a restrictive and obstructive lung disease in the studied cases with predominance of the restrictive pattern.

Pulmonary functions in patients with beta-thalassemia major were the subjects of many previous studies (15), (16), (17), that reported the presence of restrictive lung disease.

Fung et al. (15), found that the means for FEV1 and FVC for thalassemia group were significantly smaller than those for the control group. However, difference in FEV1/FVC was not statistically significant (P>0.05).

Cunningham et al. (17), explained the restrictive lung disease to be not only due to pulmonary hemosiderosis but also due to transfusion dependent chronic volume overload with decrease of lung capacity causing progressive restriction.

Vittorio et al. (5), found that hypoxemia is a consistent abnormality in patients with beta-thalassemia major that stimulates excessive alveolar growth. This hypoxia induced alveolar proliferation is both excessive (with no corresponding increase in bronchial and bronchiolar tree) and aberrant since some of the proliferating alveoli are not in direct continuity with the bronchial tree. This results in distal gas trapping and air way obstruction.

Carnell; et al. (18), found that restrictive disease and reduced lung diffusing capacity are the predominate abnormalities of pulmonary function in patients
with thalassemia major. They suggested that these pulmonary dysfunctions are due mainly to lung fibrosis and/or interstitial edema related to iron overload.

**CONCLUSION**

From our data we conclude that clinically patients with B-thalassemia major have abnormal left and right dimensions as well as relaxation abnormalities which may be a reflection of early myocardial damage. This early damage is detectable by a widely applicable echocardiographic method which may be more appropriate for those developing countries with a population affected by thalassemia.

Also the present study has shown that restrictive disease and reduced lung diffusing capacity are the predominant abnormalities of pulmonary function in patient with thalassaemia major due to lung fibrosis and/or interstitial edema related to iron overload, hypoxemia, cardiac damage, decreased alveolar growth and pulmonary vascular involvement by microthrombosis.


الملخص العربي

مقدمة:

يعتبر مرض السلاسيميا من اهم انواع الأنيميا التي ينتج عنها تثبيت خلايا الدم الحمراء وينتشر هذا المرض في الأقطار التي تطل على البحر الأبيض المتوسط نتيجة لخلل جيني متواج. وتؤدي عملية نقل الدم المتعددة لهؤلاء المرضى الى زيادة نسبة الحديد بالدم مما يؤدي إلى ترسيب في الأعضاء المتعددة من جسم الإنسان. ويؤدي ترسب الحديد بالقلب إلى فشل وظيفي في البطينين الأيمن والأيسر كما يترسب في الرئتين ويؤدي إلى فشل الوظائف التنفسية.

الهدف من البحث: يهدف البحث إلى الاكتشاف المبكر للعطل الوظيفي في القلب وكذلك الرئتين في مرضى السلاسيميا البحر المتوسط.

طرق البحث: تم إجراء البحث على 52 طفلاً يتراوح اعمارهم بين 5-15 سنة مصابون بأنيميا البحر المتوسط ومن المترددين على مستشفى بنها الجامعي كما تم إجراء البحث على 52 طفلاً طبيعياً من نفس السن والنوع كمتطوعين. وتم أخذ التاريخ المرضي لكل طفل وعمل كشف طبي كامل، وعمل رسم قلب، وموجات فوق صوتية على القلب وعمل اختبار للوظيفة التنفسية للرئتين.

نتيجة البحث:

وتبين من البحث الآتى:

زيادة في حجم البطين الأيسر أثناء الانقباض والانبساط في مرضى السلاسيميا البحر المتوسط بالمقارنة بالمتطولين، كما وجد أن 20% من المرضى يعانون من خلل في الوظيفة الانبساطية للبطين الأيمن. كما أثبت البحث أن هناك 44% من المرضى المصابين بأنميما البحر المتوسط يعانون من تضخم في البطين الأيسر، ونسبة 8% تضخم بالبطين الأيمن. كما أثبت البحث وجود خلل في الوظيفة التنفسية للرئتين في مرضى أنيميا البحر المتوسط بالمقارنة بالمتطوعين.

الخلاصة:

إن مرضى أنيميا البحر المتوسط يعانون من خلل في الوظيفة الانبساطية للبطين الأيمن. وزيادة في حجم البطين الأيسر والأيسر ويمكن بمتابعة هؤلاء المرضى الاكتشاف المبكر لهذا الخلل من خلال عمل متابعة بالموجات فوق الصوتية على القلب. كما أن هؤلاء المرضى أيضاً يعانون من خلل في الوظائف التنفسية للرئتين نتيجة لتوريس الحديد بهما مما يؤدي إلى حدوث تليف في نسيج الرئتين.