Cardiopulmonary Evaluation in Pediatric Patients with B-thalassemia and Sickle Cell Disease

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Abstract: Background: Cardiopulmonary complications have been documented by certain studies among adult patients with chronic hemolytic anemia on regular blood transfusion & thought to be a leading cause of death. Other studies suggested that these abnormalities start in childhood. We investigated the cardiopulmonary function in pediatric patients with β-thalassemia & sickle cell disease. We studied also the correlation between the cardiopulmonary abnormalities & both the severity of the disease & the degree of iron overload. Material & Methods: 26 pediatric patients were enrolled in this study, including 16 patients with β-thalassemia (14 males & 2 females, mean age 9.3 ± 3.2 yrs) & 10 patients with Sickle cell disease (SCD) (5 males & 5 females, mean age 11.5 ± 2.8 yrs). 20 age-matched healthy children were included as control. All were subjected to pulmonary function tests (FVC%, FEV1, FEF75, PEF) & echocardiography examination (ESD, EDD, FS%, EF%, E/A ratio, RVD & PASP). Results: Both groups; β-thalassemia & SCD patients had significantly lower FVC%, FEV1, FEF75, PEF in comparison to normal control (p-value < 0.05) while FEV1/FVC ratio was within normal suggesting early restrictive changes. Only 4 patients with β-thalassemia (25%) & 2 patients with SCD (20%) had FVC% & FEV1 lower than 80% with FEV1/FVC ratio > 75 reflecting evident restrictive lung abnormalities. Echocardiography examination revealed preserved cardiac function among all patients while pulmonary artery pressure (PASP) showed significant elevation. Mean value in β-thalassemia 36.14 ± 4.1 mmHg & in SCD 39.52 ± 5.6 mmHg (P-value < 0.001). Conclusion: pulmonary function tests abnormalities & pulmonary hypertension in β-thalassemia & SCD start early in childhood. So, regular assessment of cardiac & pulmonary functions is essential among those patients. Proper iron chelation therapy & regular use of L-carnitine may be beneficial in prevention & improvement of these complications.

Key words: PFTs, Echocardiography, β-thalassemia, SCD

INTRODUCTION

β-Thalassemia & Sickle Cell Disease (SCD) are two hereditary disorders that result from haemoglobin abnormalities and manifest clinically by chronic haemolytic anaemia. 

Regular blood transfusion is mandatory for long term survival among patients with β-thalassemia, but over a period of years, this causes a secondary state of tissue iron overload that can result in cardiomyopathy & heart failure.

Also, several studies on cardiac function in patients with SCD demonstrated abnormalities of both systolic and diastolic function including elevated left ventricular myocardial performance index (LVMPI) on chronic transfusion protocols.

Regarding pulmonary function abnormality, patients with β-thalassemia often present with a restrictive pattern due to several pathogenetic factors. Adults with SCD have also restrictive lung function abnormalities which are thought to result from repeated lung damage caused by episodes of pulmonary vaso-occlusion, such episodes start in childhood.

These vaso-occlusive crisis are repeated attacks of severe pain due to microvascular entrapment of erythrocytes & leucocytes, which obstruct blood flow & bring about organ ischemia. Precapillary obstruction by rigid deformed erythrocytes with a high content of Hb S polymer probably also contributes to occlusion of the microcirculation.

Another possible complication of both β-Thalassemia & SCD is pulmonary hypertension (PHT). In SCD, a major risk of PHT is the severity of haemolytic anaemia determined by steady – state Hb levels & levels of lactate dehydrogenase, indirect bilirubin & reticulocytes. In β-thalassemia, the...
pathogenesis of PHT is not well understood. Thromboembolism has been postulated as one of the causative factors & certain studies had underscored the role of platelet activation in the development of PHT & stressed its occurrence even among patients who are regularly transfused. (9)

Aim of Work: The aim of the current study was to evaluate the cardiopulmonary function in paediatric patients with β- Thalassemia & SCD and to study the correlation between the cardiopulmonary compromise and both:

1. The severity of the disease assessed by the duration of illness, Hb level & frequency of vasoocclusive crises (VOC) in SCD

2. The degree of iron overload assessed by serum ferritin level.

MATERIALS AND METHODS

26 patients were enrolled in this study. They were diagnosed as chronic haemolytic anaemia & subdivided into 2 groups:

Group 1: included 16 patients with β-Thalassemia, their mean age was 9.3 ± 3.2 years & they were 14 males & 2 females, on regular blood transfusion with mean frequency 5.3 ± 5.6 times/year

Group 2: included 10 patients with Sickle Cell Disease (SCD). Their mean age was 11.5 ± 2.8 years & they were 5 males and 5 females

The mean frequency of blood transfusion/year was 1.88 ± 1.5 while the frequency of VOC/year was 1.55 ± 1.48

All patients in the two groups were on the following treatment:

Folic acid, Vitamin B12, & L-Carnitine with a dose 50mg/kg/d & 8 patients, those with high serum ferritin level, are on oral iron chelation in the form of deferriprone 75mg/kg/d.

All patients were recruited from the paediatric haematology clinic, Beni Sueif University Hospital.

20 age matched normal children were also recruited as control.

Informed consent was taken from the parents of all participating children & the Hospital Ethics Committee approved the study.

All patients & controls were subjected to:

1. Full history taking including any chest or cardiac symptoms.
2. Thorough clinical examination.
3. Complete blood picture.
4. Serum ferritin.
5. Pulmonary function tests:

Flow-volume spirometry was performed to all patients using JAEGER master screen-105, with the subject seated using the ATS 1994 criteria for performing the manoeuvre (10). Nose clips and disposable bacterial filters were used.

At least-three technically acceptable measurements were performed with the maximum of five efforts the highest was recorded.

Well trained resident and a nurse performed the measurement. The calibration of the spirometer was checked with 3 litres. Calibration syringe once a day and when the spirometer software requested calibration. The lung function results were expressed a percentage for height using the data of Rosenthal et al (11).

FVC with timed measurements of the expiratory air flow as forced expiratory volume in one second was expressed as an absolute volume FEV<sub>1</sub> or a percentage of the forced vital capacity FEV<sub>1</sub> /FVC%. The forced mid expiratory flow rate FEF<sub>25-75% </sub> represent the average flow over the mid portion of FVC was also recorded.

Restrictive lung disorders reduce VC however the configuration of the volume dash time relation may not be abnormal FEV<sub>1</sub> /FVC% remain normal or even exceed normal values. Often because of reduced VC, FEF<sub>25-75% </sub> is also less than predicted.

A discrepancy between FVC and VC appears in obstructive diseases of the air ways, expiration may continue for 10-12 seconds these changes in respiratory air flow reduces FEV<sub>1</sub>, FEV<sub>1</sub> /FVC% and FEF<sub>25-75%</sub>.

Examining other spirometric variables was beyond the scope of the study.

6-echocardiographic Evaluation: LV diastolic function was assessed by trans-mitral Doppler flow (continuous and pulsed) in terms of ratio between peak velocities of E and A waves i.e., E/A ratio.

The normal pattern of LV filling is altered in many patients with cardiac diseases. Three abnormal patterns (in patients with sinus rhythm without mitral stenosis) have been identified indicating progressively greater impairment of diastolic function (13).

The first abnormal pattern of filling has been termed “abnormal relaxation” in which there is reduced peak rate and amount of early LV filling and the relative importance of atrial filling is enhanced. This results in a reversed E/A ratio of less than 1.0 (i.e. E < A).

The second pattern of abnormal filling has been termed “pseudonormalization”. This pattern, in which the E/A ratio is greater than 1.0 (as in normal), is seen in patients with more severe impairment of diastolic performance than the abnormal relaxation pattern. It is due to a restoration of the normal early diastolic LV pressure gradient due to an increase in LA pressure. It is distinguished from normal by a more rapid rate of
RESULTS AND DISCUSSION

The current study included 16 patients with β-thalassemia & 10 patients with SCD. The pulmonary functions results revealed that 4 patients with β-thalassemia (25%) had PFT abnormalities with reduced FVC and FEV₁ less than 80% and the FEV₁/FVC ratio was more than 75% reflecting restrictive lung abnormalities. All lung volumes including FVC, FEV₁, PEF and FEF 75% were significantly lower among β-thalassemia in comparison to normal control. Suggesting early restrictive changes in that patient. The mean values are shown in table III. But no significant correlation was found between FVC or FEV₁ and either the severity of the disease or serum ferritin level.

Our results agreed with previous works, like Abu-Ekteish, et al.¹⁷ who reported a predominantly restrictive abnormalities in 35% of β-thalassemia children included in the study with significant reduction in residual volume (RV), total lung capacity (TLC) & peak expiratory flow (PEF) with an FEV₁/FVC ratio of more than 75%. The same author reported obstructive airway disease in 15% only of the studied group with reduced FEV₁/FVC & an FEV₁/FVC less than 75%.

Also, Arora, et al.⁶ reported restrictive abnormalities in PFT in 86.6% of cases with decrease in all lung volumes with normal FEV₁/FVC ratio (> 0.75). Both authors suggested certain pulmonary parenchymal pathology however its nature is obscure & they found no significant correlation between these restrictive abnormalities & serum ferritin level. While Kanj, et al.¹¹ concluded that, the restrictive PFTs abnormalities in β-Thalassemia were correlated with serum ferritin level.
Fig. 1: Mean FEV1 among the study groups
FEV1= Forced expiratory volume in first second
SCD=Sickle cell disease

Fig. 2: Mean FVC among the study groups
FVC= Forced vital capacity
SCD=Sickle cell disease

Fig. 3: Mean PASP among the study groups
PASP= Pulmonary Artery Systolic Pressure
SCD=Sickle cell disease
Regarding PFTs results among SCD patients, their mean values were shown in table IV. All parameters were significantly reduced than the mean values of the normal controls.

Two patients only (20%) had low FEV₁ & FVC (less than 80%) & FEV₁/FVC ratio was>75% reflecting evident restrictive lung abnormalities.

No significant correlation was found between these results and the severity of the disease or serum ferritin level. These results were consistent with Hijazi, et al[18] who reported that children with SCD have early restrictive pulmonary function pattern with mean values of FVC= 83.2 ± 11.9 % FEV₁= 86.4 ± 11.5 with no significant difference between those with frequent VOC & those with infrequent crisis.

This observation underscores the early occurrence of pulmonary involvement, even in patients with otherwise relatively mild SCD.

Again, Sylvestre, et al[9] reported significant reduction in PFT parameters among children with SCD with restrictive pattern & suggested that these abnormalities may become more prominent with increasing age.

An important finding in the current study is the incidence of chest & cardiac symptoms as shown in table I. Although no patient gave history of haemoptysis or acute chest syndrome & the dyspnea and physical intolerance could be explained by the anemia itself, this doesn't exclude that the ongoing lung pathology had significant impact on lung function parameters.

This is consistent with Azarkeirar, et al[15] who concluded that the lung may be considered a site for organ dysfunction, and alteration of pulmonary function may be expected in transfusion-dependant patients in spite of no pulmonary symptoms or normal chest X-ray.

Echocardiographic assessment of our patients revealed: preserved cardiac function among both β-Thalassemia & SCD patients.

Although there was significant difference between ESD & EDD in β-Thalassemia & normal control, this doesn't reflect any clinical significance as all parameters among β-Thalassemia patients were within normal. Also, in SCD patients, all parameters were within normal with no statistical significant difference in comparison to normal controls.

Our results were consistent with Seliem, et al[20] who reported that, left ventricular systolic performance is well preserved in patients with thalassemia & SCD during early childhood. However several studies had documented abnormalities of both systolic & diastolic function including LVMI in both adults and paediatric patients with SCD [3,21] and those with β-Thalassemia [23].

Also, Lamers, et al[23] reported significant left ventricular dilatation and increased LV mass with impaired contractility in SCD patients.

Our findings can be explained by the regular use of L-Carnitine with a dose: 50 mg/Kg/d by our patients. L-Carnitine was proved to have a protective effect on cardiac function due to its role in fatty acid oxidation. [24]

The other important issue is the proper iron chelation therapy received by those patients in the form of oral deferiprone 75mg/Kg/d. This helped markedly in reduction of serum ferritin level in those with recurrent blood transfusion. However, the regular assessment of cardiac status in those patients is essential for early recognition of early stages of heart disease allowing prompt intervention, as the ongoing pathology increases with age.

Concerning the pulmonary artery systolic pressure (PASP), The current study documented significant elevation among both β-Thalassemia & SCD patients in comparison to normal healthy controls. This finding agreed with several studies which reported PHT either in β Thalassemia[9,24] or SCD [21,26,27]

The pathogenesis of PHT which is a serious complication in β-Thalassemia is not well understood. Thromboembolism has been postulated as one of the causative factors.[9]

While in SCD, several mechanisms may contribute to the development of PHT like, intravascular haemolysis, iron overload, hepatitis C or nodular hepatic regenerative hyperplasia can cause liver dysfunction leading to Porto pulmonary HTN or chronic renal failure. In situ thrombosis & pulmonary emboli are often identified clinically and at autopsy.[10] It is important to mention that, despite PASP are much lower than those in idiopathic or hereditary pulmonary HTN, in SCD, borderline or mild pulmonary HTN is associated with an extremely high risk of death[26,29].

Again, regular use of L-Carnitine by those patients is beneficial as it has been proved to reduce PASP especially among β Thalassemia patients[24]

Conclusion & Recommendation: Pulmonary function tests abnormalities & PHT start early in childhood in β-thalassemia & SCD patients.

Early identification, prevention and expert management of these complications by haematologists, pulmonologists & cardiologists will be a challenge as the population of patients with β-Thalassemia & SCD ages and increases worldwide.

Proper iron chelation therapy & regular use of L-Carnitine in those patients are beneficial in prevention & improvement of cardiopulmonary complications.
Table 1: Descriptive clinical data of the studied groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group1: β Thalassemia N=16</th>
<th>Group2: SCD N=10</th>
<th>Group3: Normal control N=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>9.3 ± 3.2</td>
<td>11.5 ± 2.8</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>M: 14= 87.5%</td>
<td>M: 5 50%</td>
<td></td>
</tr>
<tr>
<td>F: 2 =12.5%</td>
<td></td>
<td>F: 5 50%</td>
<td></td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>5.47 ± 3.19</td>
<td>4.8 ± 3.2</td>
<td></td>
</tr>
<tr>
<td>Frequency of blood transfusion/year</td>
<td>5.31 ± 5.6</td>
<td>1.88 ± 1.5</td>
<td></td>
</tr>
<tr>
<td>Frequency of VOC/year</td>
<td></td>
<td>1.55 ± 1.45</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12 = 75%</td>
<td>5 = 50%</td>
<td></td>
</tr>
<tr>
<td>Physical intolerance</td>
<td>12 = 75%</td>
<td>4 = 40%</td>
<td></td>
</tr>
<tr>
<td>Chronic cough</td>
<td>2 = 12.5%</td>
<td>0 = 0%</td>
<td></td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>0 = 0%</td>
<td>0 = 0%</td>
<td></td>
</tr>
<tr>
<td>Acute chest syndrome</td>
<td>0 = 0%</td>
<td>0 = 0%</td>
<td></td>
</tr>
<tr>
<td>HSM: Mild</td>
<td>2 = 20%</td>
<td>8 = 80%</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>2 = 12.5%</td>
<td>0 = 0%</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>6 = 37.5%</td>
<td>8 = 50%</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Descriptive laboratory data of the studied groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group1: β Thalassemia N=16</th>
<th>Group2: SCD N=10</th>
<th>Group3: Normal control N=20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb gm/dL</td>
<td>7.63 ± 1.39</td>
<td>8.14 ± 0.8</td>
<td>11.3 ± 0.5</td>
</tr>
<tr>
<td>Feritin ng/mL</td>
<td>575.16 ± 323.8</td>
<td>248.1 ± 313.8</td>
<td>112 ± 25.3</td>
</tr>
<tr>
<td>Hb A1</td>
<td>68.43 ± 15.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb A2</td>
<td>3.13 ± 1.81</td>
<td>3.68 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>Hb F</td>
<td>28.43 ± 15.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb S</td>
<td></td>
<td>96.32 ± 2.1</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Statistical comparison between Pfts of β Thalassemia (Group1) & Normal control (Group3)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group1: β Thalassemia N=16</th>
<th>Group3: Normal control N=20</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC %</td>
<td>81.98 ± 14.2</td>
<td>105.83 ± 6</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>FEV1 %</td>
<td>90.07 ± 16.26</td>
<td>117.7 ± 3.3</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>FEF75</td>
<td>79.3 ± 31.7</td>
<td>112.9 ± 20</td>
<td>0.002*</td>
</tr>
<tr>
<td>PEF</td>
<td>86.8 ± 20.1</td>
<td>112.8 ± 18.2</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>93.12 ± 4.8</td>
<td>95.84 ± 2.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

*P-value < 0.005 = significant  
*P-value < 0.001 = highly significant  
*P-value > 0.05 = Non Significant (NS)  
FVC= Forced vital capacity  
FEV1= Forced expiratory volume in first second  
FEF= Forced expiratory flow  
PEF= Peak expiratory flow
### Table 4: Statistical comparison between PFT of SCD & Normal control

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 2: SCD No=10</th>
<th>Group 3: Normal control No=20</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>89.24 ± 7.6</td>
<td>105.83 ± 6</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>FEV1</td>
<td>90.38 ± 9.8</td>
<td>117.7 ± 3.3</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>FEF75</td>
<td>78.77 ± 12.9</td>
<td>112.9 ± 20</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>PEF</td>
<td>86.27 ± 17.09</td>
<td>112.8 ± 18.2</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>88.1 ± 7.9</td>
<td>95.84 ± 2.8</td>
<td>0.022*</td>
</tr>
</tbody>
</table>

*P-value < 0.05 = significant
*P-value < 0.001 = highly significant
P-value > 0.05 = Non Significant (NS)

FVC=Forced vital capacity
FEV1=Forced expiratory volume in first second
PEF=Peak expiratory flow

### Table 5: Statistical comparison between Echocardiographic parameters of β-Thalassemia pts & Normal control

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1: β-Thalassemia No=16</th>
<th>Group 3: Normal control No=20</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESD (cm)</td>
<td>2.7 ± 0.2</td>
<td>2.5 ± 0.2</td>
<td>0.03*</td>
</tr>
<tr>
<td>EDD (cm)</td>
<td>4.3 ± 0.34</td>
<td>4.04 ± 0.3</td>
<td>0.02*</td>
</tr>
<tr>
<td>Fs (%)</td>
<td>37.5 ± 4.8</td>
<td>32.4 ± 2.8</td>
<td>NS</td>
</tr>
<tr>
<td>EF (%)</td>
<td>69.31 ± 3.7</td>
<td>66.6 ± 4.5</td>
<td>NS</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.3 ± 0.1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>PASP (mmHg)</td>
<td>36.14 ± 4.1</td>
<td>21.1 ± 4</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>RVD (cm)</td>
<td>1.69 ± 0.1</td>
<td>1.8 ± 0.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

ESD = Lt ventricular End Systolic Diameter
EDD = Lt ventricular End Diastolic Diameter
Fs = Fractional shortening
EF = Ejection Fraction
PASP = Pulmonary Artery Systolic Pressure
RVD = Rt Ventricular Diameter

*P-value < 0.05 = significant
*P-value < 0.001 = highly significant
P-value > 0.05 = Non Significant (NS)

### Table 6: Statistical comparison between Echocardiographic parameters of SCD pts & Normal controls

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 2: SCD No=10</th>
<th>Group 3: Normal control No=20</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESD (cm)</td>
<td>2.5 ± 0.3</td>
<td>2.5 ± 0.2</td>
<td>NS</td>
</tr>
<tr>
<td>EDD (cm)</td>
<td>4.1 ± 0.4</td>
<td>4.04 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Fs (%)</td>
<td>34.2 ± 5.1</td>
<td>32.4 ± 2.8</td>
<td>NS</td>
</tr>
<tr>
<td>EF (%)</td>
<td>64 ± 5.2</td>
<td>66.6 ± 4.5</td>
<td>NS</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.36 ± 0.1</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>PASP (mmHg)</td>
<td>39.52 ± 5.6</td>
<td>21.1 ± 4</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>RVD (cm)</td>
<td>1.7 ± 0.3</td>
<td>1.8 ± 0.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

ESD = Lt ventricular End Systolic Diameter
EDD = Lt ventricular End Diastolic Diameter
Fs = Fractional shortening
EF = Ejection Fraction
PASP = Pulmonary Artery Systolic Pressure
RVD = Rt Ventricular Diameter

*P-value < 0.05 = significant
*P-value < 0.001 = highly significant
P-value > 0.05 = Non Significant (NS)
ABBREVIATIONS

FVC=Forced vital capacity  
EDD=End diastolic diameter  
EF=Ejection fraction  
ESD=End systolic diameter  
FEF=Forced expiratory flow  
FEV1=Forced expiratory volume in first second  
FS=Fractional shortening  
HSM=hepatosplenomegaly  
LV MPI=left ventricular mass index performance  
PASP=Pulmonary artery systolic pressure  
PEF=Peak expiratory flow  
PFTs=Pulmonary function tests  
PHT=pulmonary hypertension  
RV=residual volume  
RVD=Right ventricular diameter  
SCD=Sickle cell disease  
TLC=total lung capacity  
VOC=vaso occlusive crisis

REFERENCES


