Spirometry and Cardiopulmonary Exercise Performance in Patients with Thalassemia Major

MONA EL-TAGUI, M.D.; KHALED SALAMA, M.D.; HASSAN M. SALAMA, M.D. *;
MONA M. MAHMOUD, M.D.; HOSSAM H. MASSOUD, M.D. **;
MOHAMAD EL-BATANONY, M.D. *** and AZZA ABDEL MEGIUD, M.D.
The Departments of Pediatrics, Chest **, Occupational Medicine ***, Faculty of Medicine, Cairo University and Pediatrics *, National Research Center, Cairo.

Abstract

Background: Lung function abnormalities in patients with thalassemia major are various, complex and of different etiological backgrounds.

Methods: To evaluate the pulmonary function changes during both rest and integrated cardiopulmonary exercise in patients with thalassemia major, we studied 30 thalassemia major cases with mean age of 18 ± 13.34 years. Nineteen healthy subjects were enrolled as a control group. Routine laboratory tests as well as assessment of pulmonary function test during both rest and integrated cardiopulmonary exercise were performed for cases and controls.

Results: Both forced vital capacity (FVC) and forced expiratory flow in the first second (FEV1) were significantly reduced in cases than in controls (p<0.01 for both), pointing to a restrictive pulmonary dysfunction. Seventy percent of cases had FVC below the normal predicted value. Functional capacity, anaerobic threshold and O2 pulse were significantly reduced in cases than controls (p<0.05). There is a statistically significant inverse correlation between serum ferritin levels and functional capacity.

Conclusions: In the studied thalassemics, restrictive pattern of pulmonary dysfunction is the predominant abnormality. Poor cardiopulmonary exercise performance occurs and is multifactorial.

Key Words: Lung function abnormalities – Thalassemia major – Spirometry – Cardiopulmonary exercise.

Introduction

PATIENTS with beta-thalassemia often present with a restrictive pattern at pulmonary function tests [1].

To maintain adequate hemoglobin concentration and prevent the adverse effects associated with this disorder, patients receive regular transfusion. These transfusions lead to accumulation of iron in different tissues and subsequent damage and dysfunction of these systems. The heart, liver and endocrine organs are targets most frequently involved. Iron chelation with desferrioxamine has become standard therapy in these patients [2].

Although cardiac dysfunction is a major cause of death in patients with β-thalassemia major, pulmonary involvement has been described [3]. Iron deposition has been observed in postmortem examination of patients receiving multiple blood transfusions [4]. This deposition can cause lung dysfunction most likely of restrictive pattern. Damage to the lung can also be induced by recurrent transfusion [5].

Lung function abnormalities that are associated with thalassemia major are variable in etiology that is yet undetermined [6].

Several investigators provided evidence supporting obstructive defect [7] while others have concluded that restrictive disease is more common [8].

The aim of this study was to evaluate the pulmonary function changes during both rest and integrated cardiopulmonary exercise in patients with thalassemia major and to correlate their pulmonary function with some clinico-laboratory parameters of these patients.

Patients and Methods

Thirty cases of thalassemia major attending the pediatric hematology clinic at New Children Hospital Cairo University were enrolled in this study. They were 17 males and 13 females with male: female ration 1.3: 1, age ranged from 8 to 23 years with a mean value 18.00 ± 12.34. Nineteen healthy age matched control subjects were enrolled in the study.
Inclusion criteria of patients include:
- Thalassemia patients with history of blood transfusion for at least 10 years.
- Hb F should be more than 4%.
- The patients should be on iron chelation therapy.

Exclusion criteria of patients include:
- Patients with history of bronchial asthma or any chest problems.
- Patients with cardiac problems as arrhythmias or heart failure.
- Patients with limiting neurological disorders.

Both cases and controls were subjected to the following:
- Full clinical evaluation, routine laboratory tests and assessment of pulmonary function test during both rest and integrated cardiopulmonary exercise were performed for cases and controls.
- Spirometry and integrated cardiopulmonary exercise were made at the fitness and rehabilitation unit, occupational medicine, Cairo University.

The cardio-pulmonary exercise (CPX) system applied by Med Graphics includes the Gas Analyzer module, flow/waveform module and computer with colored monitor and a keyboard, connected to HP laser printer and an electronic ergometer.

This system receives the patient's data including name, age, sex, height in cm and weight in kg. Automatically the predicted values for resting ventilatory function (spirometry) and for exercise parameters are displayed.

Regarding spirometry; our subjects performed forced vital capacity (FVC) maneuver, slow vital capacity (SVC) maneuver and maximum voluntary ventilation (MVV) maneuver.

At least three trials were performed (the computer displays each attempt as absolute values, percentage of the predicted and volume-time curve). The best trial was then selected.

Exercise was performed using cycle ergometer in an air-conditioned laboratory Fitness and Rehabilitation unit. The patient was asked to breathe through face mask which is connected to mouth piece. A sample line was used for connecting the mouth piece to the gas analyzer module of the cardio O₂ system. This allows breath by breath analysis.

Ten ECG electrodes (six for chest and four-limbed lead) were connected to allow monitoring of any abnormalities in the ECG. During exercise, blood pressure was recorded automatically every one minute using an electronic sphygmomanometer.

The patient was allowed 2 minutes free wheeling with all the connections on and then the load was increased by the bike according to the selected protocol, (10-watts ramping protocol every 30 seconds). All subjects were asked to perform the test maximally the patient exercises till reaching the maximal oxygen consumption (VO₂ max) or if there was any indication for termination. Period of 2 minutes was allowed during which the patients pedal against small load (25 watts) before terminating the exercise.

The data collected by different devices were sent to the computer which integrated them to produce further relations (e.g., oxygen pulse) and displayed the data on the screen as a graph and values. This allowed real time monitoring of the patient parameters. These parameters include oxygen consumption (VO₂ max), carbon dioxide (VCO₂) respiratory rate (RR) tidal volume (VT), heart rate (HR) blood pressure (BP) O₂ consumption (VO₂/kg/min) and O₂ pulse (VO₂/Hr).

The test was terminated in 8 patients who had promoted fatigue, leg pains, technical problems and upon patient request.

Statistical methods: All patients’ data were tabulated and processed using SPSS (12.0). Quantitative variables were expressed using mean and standard deviation, they were compared using t-student’s test (paired and unpaired). ANOVA test was performed to compare more than two groups. Pearson correlation was used to correlate two quantitative variables. Qualitative variables were compared using Chi-square test or Fischer’s exact test when appropriate. In all tests, p value considered significant when <0.05 and considered highly significant if <0.01.

Results

The study included 30 β thalassemia major patients aged from 8-23 years with mean value (18.00±12.34) 17 males, 13 females. Hemoglobin level ranged from 5.3g/dl to 7.5g/dl with mean value 6.35g/dl. Mean corpuscular volume (ranged from 59-77 fl) with mean value 62.7 fl. Serum ferritin level ranged from 750ng/dl to 4687ng/dl with mean value 2895.23ng/dl. Only four patients were properly chelated with serum ferritin less than 1500ng/dl. Hemoglobin F levels ranged from 4.1-100% with mean value 36.2%.
Seventy percent of patients showed restrictive pattern of resting ventilatory functions, (impaired forced vital capacity) while 3.33% showed obstructive pattern (impaired FEV1/FVC) and 3.33% showed mixed restrictive and obstructive patterns. MVV was low in 76.66% while FEF was low in 30% of cases.

Among cases with restrictive pattern of resting ventilatory functions, 11/21 (52.4%) had mild restrictive pattern as their FVC was between 70-80% of predicted value while 7 (35%) showed moderate restrictive pattern as their FVC was 60-70% of predicted value 3 (12.6%) had severe restrictive pattern as their FVC was below 60% of the predicted value.

In the control group 17/19 (89.45) had normal resting ventilatory functions, one showed restrictive pattern and one showed obstructive pattern. MVV was impaired in 26.3% of controls while FEF was impaired in 21.05%.

Table (1) compares resting pulmonary function tests in cases and controls. The percentages of SVC, FVC and FEV1 in cases were significantly lower than controls (p<0.01).

Regarding cardiopulmonary exercise testing 22 cases were fit to perform and complete the test. One patient (4.5%) had normal functional capacity (VO2max), while 21 patients (95.5%) had low functional capacity. Anerobic threshold was normal in 8 patients while it was low in 14 patients, breathing reserve was normal in all patients. Maximal O2 pulse was low in 20 patients and it was normal in one patient.

In the control group, the functional capacity was normal in 10 subjects while it was low in 5. Anerobic threshold was normal in all controls; maximal respiratory rate was abnormally high in 4 controls. Breathing reserve was low in one subject while maximal O2 pulse was low in 3 of the controls.

Table (2) shows the comparison of cardiopulmonary exercise testing parameters between cases and controls. All parameters were significantly different in cases than controls.
Discussion

Studying the resting pulmonary function tests, it was found that there is a reduction in FVC below 80% of predicted value in 70% of cases compared to 5.3% of controls (highly significant difference). This goes with the results obtained by Arora et al., who found that 86.6% of his thalassemic patients had significant reduction in FVC [8]. Also Luyt et al., reported significant reduction of mean FVC in all of his 15 patients examined [10]. These results indicate a predominantly restrictive lung disease in multitranfused thalassemic patients and this was approved by the studies done by Filosa et al., Carnelli et al., and Jamal et al., who reported the presence of restrictive pattern of lung dysfunction in thalassemics [11-13]. An Italian team performed a longitudinal study of pulmonary function in asymptomatic, non-smoking patients with beta-thalassemia major, in 38.8-55.5% of patients; a restrictive pattern was found [1].

In this study, 52.4% of patients examined had mild reduction of FVC i.e. FVC 70-80% of predicted value and this result is near to the result obtained by Bacalo et al., 1992 who reported that FVC was mildly reduced in all his 17 patients with thalassemia major [14].

On correlating FVC to different study parameters, no significant correlations were found between FVC and patients’ age, Hb%, serum ferritin level or HbF concentration. These were points of many debates in different studies. Jamal et al., and Abu-Ekteish et al., agreed with our results and they could not find any correlation between lung dysfunction and serum ferritin levels in the patients [13,15]. Luyt et al., Tai et al., 1996 and Arora et al., also reported that pulmonary functions do not correlate with age or serum ferritin level [4,8,10]. Other authors do not approve with these conclusions. Kanj et al., found a significant correlation between serum ferritin level and presence of restrictive lung disease [16]. Filosa et al., found that the presence of a restrictive pattern is directly related to serum ferritin and patients age [11]. Also Sritippayawan et al., in 2005 concluded that restrictive lung disease is related to longer duration of transfusion and higher serum ferritin [17]. These differences may be due to the fact that patients with thalassemia major differ in chelation and that serum ferritin is not an accurate measure for assessment of total body iron and its level (being an acute phase reactant) is affected by many factors [18].

The involvement of other causal mechanisms, in addition to iron load, in the development of restrictive pulmonary abnormality in thalassemics needs to be searched for [14,19].

To evaluate patients for obstructive pulmonary function abnormality FEV1/FVC was measured and it was found to be abnormally reduced in 3.33% of cases, 3.33% had mixed obstructive and restrictive pattern in resting pulmonary function tests. Having smaller number of cases with obstructive pattern than those with a restrictive one agrees with the results obtained by Tai et al., who stated that although the predominant abnormality of pulmonary functions in thalassemics is the restrictive pattern, there is mixed restrictive and obstructive patterns in smaller numbers of cases [4]. Also, Jamal et al., reported that none of their 22 patients showed the presence of obstructive ventilatory impairment [13].

There is no significant correlation between FEV1/FVC and Hb% or HbF concentration but
there is significant inverse correlation with serum ferritin level Carnelli et al., found that Both FVC and FEV 1 were negatively correlated with transfusional iron burden [12] these findings were explained by Ooi et al., who reported the presence of pulmonary iron overload in which the high resolution CT revealed a morphological and functional correlation consistent with smaller airway disease [6].

Cardiopulmonary exercise test was performed for 22 patients who met the criteria for test completion. Functional capacity (VO$_2$ max/predicted VO$_2$ max) was significantly reduced in cases than controls and this reduction showed no significant correlation regarding the age, hemoglobin percentage and HbF concentration. Functional capacity had significant inverse correlation with the serum ferritin level. These findings were approved by Cracowski et al., who found that VO$_2$ max and subsequently functional capacity was decreased in thalassemic patients, but he found that this reduction is more in adults than in children and this is due to better compliance of these patients to chelation therapy or due to longer duration of disease [20].

These findings were similar to those of Trikas et al., regarding reduction in functional capacity in thalassemic patients but this reduction was more in adults than in children due to the duration of evolution of the disease [21], Cooper et al., have documented an impairment in functional capacity in thalassemia [22].

In the present study the O$_2$ pulse max was significantly lower in cases than in controls, there was low slope of O$_2$ pulse (VO$_2$/HR) and steeping heart rate response (only 2 patients had normal O$_2$ pulse, their Hb level was 7.5 & 7.1gm/dL). Cracowski et al., in 1998 has reached to the same result but he found that the reduction is more in adults than in children probably due to better compliance with the chelation therapy delaying the appearance of cardiopulmonary problems [20]. This goes with the result of Cooper et al., who studied such relationship extensively and proved that O$_2$ pulse is within normal in children contrary to adults where it is reduced and the reduction is associated with steeping heart rate, this low slope of O$_2$ pulse is affected principally by weight [23].

All cases expressed a breathing reserve that is higher than 40% maximal voluntary ventilation and this goes along with the results obtained by Grant et al., 1987 and Cracowski et al., 1998 [20,24].

Also thalassemics included in this study showed significantly decreased anaerobic threshold when compared with the control group. As 63.36% of cases had low anaerobic threshold, on the contrary none of the controls had low anaerobic threshold. Trikas et al., reported in his study on 40 patients with thalassemia major that patients had reduced anaerobic threshold in comparison with control subjects and this decrease can be attributed to cardiovascular dysfunction [21]. Grant et al., 1987 found the same results [24].

**Conclusion:**

Restrictive pattern of pulmonary dysfunction is the predominant abnormality in thalassemics. A small percentage of patients have mixed restrictive and obstructive patterns in resting pulmonary function test. As regards integrated cardiopulmonary exercise test, most patients have poor exercise performance (decreased functional capacity, anaerobic threshold and O$_2$ pulse).

**References**


