

EVALUATION OF PULMONARY FUNCTION IN β -THALASSEMIA MAJOR PATIENTS

Ismaeil Eidani¹, Bijan Keikhaei², Fakher Rahim³, Arezoo Bagheri⁴

ABSTRACT

Objective: To describe and quantify the functional change of the lung in patients with β -thalassemia major (TM) and determine the correlation between pulmonary function test (PFT) results with hemoglobin, ferritin and age changes.

Methodology: Pulmonary function tests were performed on 60 transfusion-dependent patients with TM, ranging in age from 10 to 45 years. Percent-predicted values for forced expiratory volume in one second (FEV1), and forced expiratory flows (FEF) 25-75% were significantly reduced, whereas forced expiratory vital capacity (FVC) and FEV1/FVC were closed to normal limits, indicating a restrictive disease. All factors including; FVC, FEV1, and FEV1/FVC, FEF 25-75% were negatively correlated with age and ferritin levels. In contrast, all factors including; FVC, FEV1, and FEV1/FVC, FEF 25-75% were positively correlated with hemoglobin (Hb). We performed linear regression analysis to study the simultaneous influence of the presence of age, ferritin, and Hb on obstructive PFT indexes.

Results: Pulmonary function test results were normal in only 32 (53.3%) of 60 patients and the rest 28 cases (46.7%) showed abnormal pulmonary function. FEV1 and FEF25%-75% have significant negative correlation with age ($r = -0.64$ $p(r) = 0.003$ and $r = -0.58$ $p(r) = 0.02$ respectively), also have significant positive correlation with Hb ($r = 0.31$ $p(r) = 0.015$ and $r = 0.33$ $p(r) = 0.01$ respectively), and only FEF25%-75% has significant negative correlation with ferritin ($r = -0.26$ $p(r) = 0.04$).

Conclusion: The present study has shown that restrictive disease and reduced lung diffusing capacity are the predominant abnormalities of pulmonary function in patients with TM. The low hemoglobin concentration and a fall in the diffusing capacity of the alveolar-capillary membrane, together with the dependence of the reduced pulmonary diffusing capacity on age and serum ferritin levels, as well as of the entity of restrictive disease on age, suggests that pulmonary dysfunctions in patients with TM are due mainly to lung fibrosis and/or interstitial edema related to iron overload.

KEY WORDS: β -thalassemia major, Pulmonary function test, Age, Hemoglobin, Ferritin.

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Correspondence

Bijan Keikhaei,
Thalassemia and hemoglobinopathies Research Center,
Ahwaz Jondishapour University of Medical Sciences,
Ahwaz, Iran.
Email: fakherraheem@yahoo.com

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INTRODUCTION

Thalassemia major (TM) is a disorder characterized by ineffective erythropoiesis, leading to impaired oxygen delivery to the tissues. Although adequate, protracted transfusion programs prevent the development of the adverse effects associated with this disorder, iron accumulation eventually occurs, in spite of concomi-

tant chelation therapy. Heart and liver dysfunction have been extensively studied owing to their early effect on survival. Pulmonary dysfunction is one of the least understood complications of α -thalassemia major, although it is not uncommon, having been reported in up to 80% of patients with the disease.^{1,2}

Reported abnormalities are varied and include restrictive lung disease,¹⁻⁶ impaired diffusing capacity of lung for carbon monoxide (DLCO),^{3,7} small-airway disease,^{4,8,9} and obstructive airway disease.^{3,4,7} Although the heart, liver, and pancreas are the target organs most frequently involved, and in which extensive iron-induced injury is regularly observed at necropsy, abnormalities of lung mechanics have been reported by almost all studies of patients with TM. However, there is no consensus about the nature, restrictive¹⁰⁻¹³ or obstructive,¹⁴⁻¹⁶ of these defects. Indeed, substantial iron deposition in the lung has been observed on postmortem examination in some¹⁷⁻¹⁹ but not in other cases.^{10,11} In addition to abnormal lung mechanics, patients with TM regularly exhibit a reduced pulmonary diffusing capacity, which in most instances is only partially due to lower hemoglobin concentration. Moreover the mechanisms leading to the fall in lung diffusing capacity have not been investigated, except in a study on a small group of young Chinese and Malay patients.³ Indeed, reduction of lung diffusing capacity could be the consequence of the fall of either the diffusing capacity of the alveolar-capillary membrane, or the pulmonary capillary blood volume, or both.²⁰

In the present study, we wanted to assess number of transfusion-dependent, thalassemic patients the predominant type of lung mechanical abnormalities, the prevalence of the reduction in pulmonary diffusing capacity and the mechanisms involved, and the relation between mechanical and diffusional alterations.

METHODOLOGY

The study included 60 diagnosed patients of TM (10–45 years) randomly selected from our institution (Research Center of Thalassemia and Hemoglobinopathies, Ahwaz Jondishapour

University of Medical Sciences, Ahwaz, Iran), whose physical characteristics are reported in Table-I. Patient with evidence of left ventricular failure, vaso-occlusive crisis during the preceding 15 days, known congestive heart failure, history of chronic obstructive pulmonary disease or poorly controlled asthma, a painful crisis and/or acute chest syndrome in the preceding four weeks, and blood transfusion in the preceding three months before performing any of the tests reported, were excluded from the study.

The patients were receiving blood transfusions at 3- to 4-week intervals, and chelation therapy with desferrioxamine via subcutaneous infusion five times a week at a dose of 40–50 mg /kg (39 patients), or deferiprone given orally at a daily dose of 75mg / kg for the entire week. Iron overload was estimated as the mean value of serum ferritin levels²¹ of 13–17 samples obtained during the preceding year. The patients had no clinical manifestations of cardiopulmonary diseases at the time of the study, which was approved by the institutional ethics committee; informed consent was obtained from patients or parents. One patient reported asthmatic episodes; nine were receiving therapy because of modest rhythm alterations and three because of left ventricular hypokinesia without pulmonary hypertension. In these patients, echocardiographic reassessment showed subsequently that digitalis had restored normal ventricular functions. Hepatomegaly was present in 30 patients, splenomegaly was present in four patients, and 26 patients had undergone splenectomy. Pulmonary function studies were performed according to recommended guidelines²² prior to blood transfusion and with a SensorMedics VMAX 22 Spirometer (SensorMedics, Yorba Linda, Calif) according to the standard American Thoracic Society protocol.²³ Results were expressed as percentages of predicted normal values.²⁴ The best values of forced expiratory vital capacity (FVC), forced expiratory volume in one second (FEV1), forced expiratory flows (FEF) 25-75%, and FEV1% were selected from three technically acceptable maneuvers, and referred to predicted values.²³

Values of all variables of interest assessed in 60 normal subjects (10–45 years) were all within $\pm 20\%$ of predicted values, mean percentage predicted values being 98% for all subjects.

Statistical Analysis: The results are presented as Means \pm Standard Error of Mean (SEM). Statistical significance was assessed by analysis of variance, the Student paired t test being used whenever appropriate. Linear regressions were computed by the least squares method and statistical assessment was made by analysis of covariance. The level of significance was taken at $p < 0.001$.

RESULTS

All of the 60 patients underwent full pulmonary function testing. Pulmonary function test results were normal in only 32 (53.3%) of 60 patients and the rest 28 cases (46.7%) showed abnormal pulmonary function. Among those 28 patients with abnormal pulmonary function, 25 patients (89.23%) showed restricted pattern. Out of those 25 only 10 patients (40%) showed moderate restricted pattern and the rest 15 (60%) showed severe restricted pattern. The means and SEM of pulmonary function test results, age, height, and weight of the patients are shown in Table-I. The means and SEM for relevant blood variables in study groups are shown in Table-II.

At simple regression analysis, there were negative correlations between FVC, FEV1, FEV1/FVC (FEV1 %), FEF25%–75%, and age of patients (Fig-1). As shown in figure 1 FEV1 and FEF25%–75% have significant negative correlation with age ($r = -0.64$ $p(r) = 0.003$ and $r = -0.58$ $p(r) = 0.02$ respectively). Also there were positive associations between FVC, FEV1, FEV1/FVC (FEV1 %), FEF25%–75%, and hemoglobin (Hb) of patients (Fig 2). As shown in Figure 2 FEV1 and FEF25%–75% have significant positive correlation with Hb ($r = 0.31$ $p(r) = 0.015$ and $r = 0.33$ $p(r) = 0.01$ respectively). Finally, there were negative correlations between FVC, FEV1, FEV1/FVC (FEV1 %), FEF25%–75%, and ferritin of patients (Fig-3). As shown in figure 3 only FEF25%–75% has significant negative correlation with ferritin ($r = -0.26$ $p(r) = 0.04$).

DISCUSSION

Abnormalities of lung mechanics have been reported by almost all investigators,¹⁰⁻¹⁷ but uncertainty persists about their nature and pathogenesis. The present spirometric data collected from the largest number of patients with TM evaluated to date have shown that the only observed lung mechanical abnormality is restrictive (Table-I). Indeed, whereas FVC, FEF25%–75%, and FEV1 were reduced, indices of large (FEV1/FVC) did not differ from predicted nor-

Table-I: Anthropometric characteristic and spirometric results

Variables	Female Patients	Male Patients
Number of subjects	29	31
Variables (Mean \pm SD):		
Age (Years)	20.03 \pm 9.23	19.75 \pm 6.56
Height (Meter)	157 \pm 16.66	152.12 \pm 14.74
Weight (Kg)	46.46 \pm 13.79	45.87 \pm 10.78
FVC (%predicted)	78.07 \pm 15.54*	75.81 \pm 19.26*
FEV1 (%predicted)	79.00 \pm 14.23*	77.42 \pm 16.48*
FEV1/FVC (%predicted)	107.00 \pm 7.16	104 \pm 1510.63
FEF25-75% (%predicted)	70.03 \pm 17.56*	67.42 \pm 15.17*

Definition of abbreviation: Forced Vital Capacity (FVC), Forced Expired Volume in one second (FEV1), Forced Expiratory Flow at 25% to 75% of FVC (FEF25 - 75%) Values represent means \pm SEM.

* Significantly different from normal ($p < 0.001$).

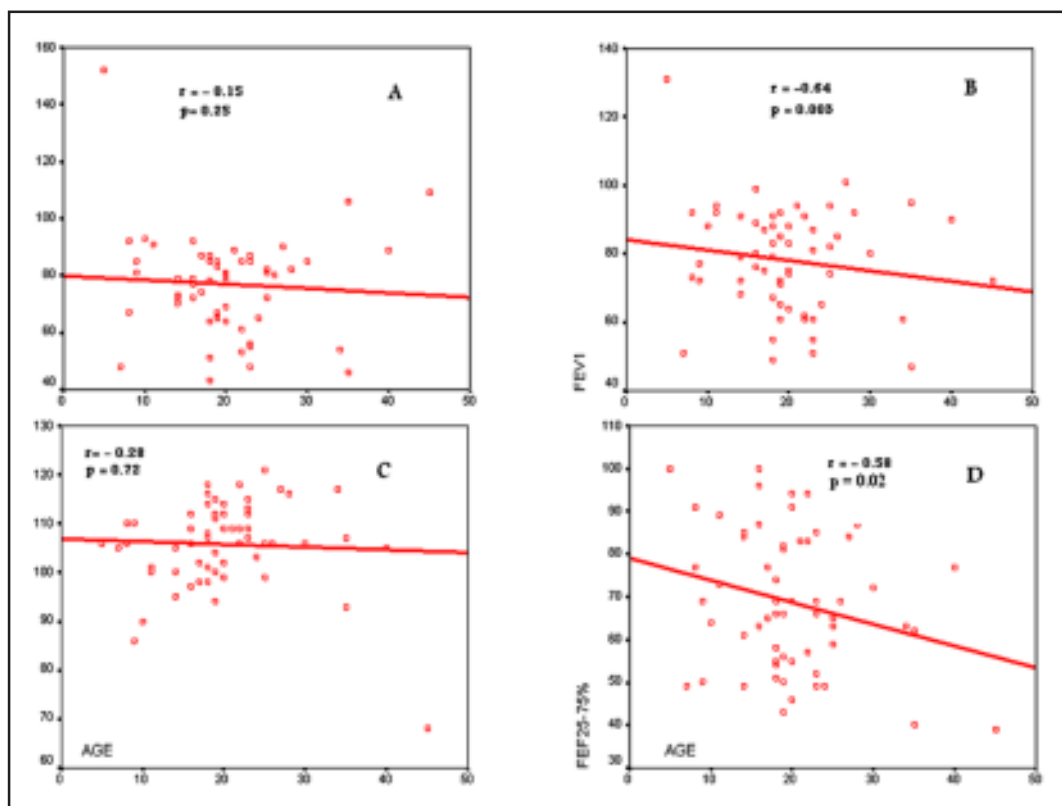
Table-II: Relevant blood variables

Variables	Female Patients	Male Patients
Number of subjects	29	31
[Hb] , g/dl	8.56±0.92	8.60±0.93
Hct	0.277±0.005	0.271±0.004
Serum ferritin, ng / μ l	2.63±0.15	2.53±0.17

Definition of abbreviations: [Hb] : hemoglobin concentration; Hct : hematocrit. Values represent means \pm SEM; they were similar between groups, but significantly different from normal values ($p < 0.001$).

mal values. Although iron deposition has been demonstrated in the lungs of patients with TM,¹⁷⁻¹⁹ a clear relation between lung hemosiderosis and restrictive disease has not been established. In line with previous studies,^{11,14} we found no significant correlation between spirometric variables and interested hematologic variables (Hb , serum ferritin, and age levels). On the other hand, these variables decreased significantly with increasing iron burden, as indexed by age (Figure-1), in agreement with the finding by Factor and coworkers¹ of a strong inverse correlation between total lung capacity

and FVC with directly measured iron burden. In the present patients, both the blood diffusing capacity and that of the alveolar-capillary membrane were decreased. The fall of the former was due to decreased [Hb], and the latter was, however, sufficient to normalize the blood diffusing capacity with partial restoration of [Hb] by transfusion. Augmentation of the capillary blood volume has often been demonstrated in patients with various cardiopulmonary diseases,^{25,26} but there was no evidence of such events in the present patients. Alternatively, the expansion of the pulmonary



Figures-1-4:

vascular bed could have been the consequence of repeated transfusions.²⁷ Finally, chronic and marked anemia could have also played a role. Arora et al.,²⁸ in a study of PFT in 30 thalassemics and 20 controls subjects have shown a restrictive abnormality in 86.6% cases. These patients were found to have a decrease in all the lung volumes namely. They showed no correlation was found between severity of restrictive disease and the serum ferritin levels and also between severity of the defect and age, number of blood transfusions received and hemoglobin at the time of doing the test. In other study on 40 children with beta-thalassemia major (23 males and 17 females) which was conducted by Abu-Ekteish et al.,²⁹ the results have shown that, no correlation was found between the severity of restrictive or obstructive disease and the serum ferritin level. Also there was a significant linear correlation between age and serum ferritin level. In agreement with this two former studies finding by Jamal and coworkers³⁰ also showed there is no correlation between lung dysfunction and serum ferritin levels in the patients. By contrast, our study show there is significant correlation between FEF25%-75% and our variables of interest (age, Hb, ferritin) and both FEV1 and FEF25%-75% with age and Hb only. In agreement with our study many researches³¹⁻³³ have shown there is a strong correlation between serum ferritin and restrictive parameters.

In conclusion, the present study has shown that restrictive disease and reduced lung diffusing capacity are the predominant abnormalities of pulmonary function in patients with TM. Apart from the contribution due to low hemoglobin concentration, the latter defect is determined by a fall in the diffusing capacity of the alveolar-capillary membrane, attributed primarily to an increase in its thickness. This, together with the dependence of the reduced pulmonary diffusing capacity on age and serum ferritin levels, as well as of the entity of restrictive disease on age, suggests that pulmonary dysfunctions in patients with TM are due mainly to lung fibrosis and/or interstitial edema related to iron overload.

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Authors:

1. Ismaeil Eidani
2. Bijan Keikhaei
3. Fakher Rahim
- 2,3: Department of Hematology and Oncology, Thalassemia and Hemoglobinopathies Research Center, Ahwaz Jondishapour University of Medical Sciences, Ahwaz, Iran
4. Arezoo Bagheri
- 1,4: Department of Internal and Respiratory Medicine, Ahwaz Jondishapour University of Medical Sciences, Ahwaz, Iran.