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β-thalassemia and pulmonary function

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Abstract

Background and Objective. **The survival of patients with β-thalassemia major and intermedia has improved considerably. This has focused attention on the long-term sequelae of the disease itself and its treatment. The effect of hemosiderosis in major organs (heart, liver, etc) are well-recognized, but the pathophyisology of any lung damage is less clearly understood. We studied lung function changes in 32 patients with β-thalassemia.**

Design and Methods. **Respiratory function tests, CO diffusion and arterial blood gas analysis were performed on 19 patients with β-thalassemia major (9 F, 10 M) and 13 with β-thalassemia intermedia (6 M, 7 F). All investigations were performed 24 hours before the patients received a blood transfusion or when they were in a stable state hematologic condition. Echocardiography was performed in all patients and the ejection fraction was employed as a measure of cardiac function.**

Results. **No patient had clinical signs of pulmonary dysfunction. Pulmonary function tests, however, showed a reduction of all main parameters (TLC, FVC, FEV1 and RV) in most patients with β-thalassemia major, indicating a restrictive type of dysfunction. The pulmonary function of patients with β-thalassemia intermedia seemed to be preserved. Arterial blood gas values were within the normal range, while in some subjects CO diffusion approached the lower limits of normality. There was no evidence that the observed abnormalities in pulmonary function were secondary to congestive heart failure.**

Interpretation and Conclusions. **Iron deposition due to repeated blood transfusions may play a central role in determining lung alterations although the majority of patients are well chelated, suggesting that more than one causal mechanisms could be involved.**

Key words: β-thalassemia, pulmonary function, restrictive ventilatory failure

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β-thalassemia major is a transfusion-dependent, inherited, chronic anemia caused by deficient production of β-globin chains that combine to form hemoglobin; consequently, free α-chains precipitate within red blood cells and most erythroid cells die in the bone marrow.

β-thalassemia intermedia is characterized by a milder phenotype with hemoglobin levels between 7-9 g/dL; patients with this phenotype usually do not require blood transfusions.

Reduced hemoglobin synthesis, ineffective erythropoiesis and short erythrocyte survival in patients with β-thalassemia major lead to severe anemia and tissue hypoxemia which can, however, be partially corrected by regular transfusions aimed at mantaining the mean Hb level around 11-12 g/dL.

Inefficient erythropoiesis persists in non-transfused or occasionally transfused patients with β-thalassemia intermedia and therefore there can be spleen enlargement. Moreover, in β-thalassemia intermedia iron absorbtion increases in the gut because of anemia and therefore accumulates, whereas in β-thalassemia major transfusion treatment increases the iron load thereby determining hemosiderosis in major organs such as the heart, liver and endocrine glands. Iron chelation with desferrioxamine (DFO) has become standard therapy to reduce these complications in patients with thalassemia major.

Since patients' survival has greatly improved over the last 10 years, multi-organ impairment due to hemosiderosis often occurs. The lungs may also be involved.

Although pulmonary dysfunction is not the most significant clinical manifestation of thalassemias, or indeed does not produce any symptoms, a certain reduction of pulmonary volumes has been reported to occur in most subjects with β-thalassemia.[1-5]

The aim of our study was to evaluate pulmonary function in both patients with β-thalassemia major and those with the intermedia form in order to determine the predominant lung dysfunction in these disorders.

Design and Methods

We measured pulmonary function in 19 patients with β-thalassemia major (9 M, 10 F, age range: 18-27 years) and 13 with β-thalassemia intermedia (6

M, 7 F, age range: 18-44 years) enrolled from the Centro Anemie Congenite, Ospedale Maggiore IRCCS in Milan, Italy. To be enroled into the study patients were required to be at least 18 year old, to be able to perform pulmonary function tests and not to be in overt cardiac failure.

The diagnosis of thalassemia was based on hematologic data and family studies. The thalassemia genotype was defined in all patients.

To maintain the Hb level at or above 11 g/dL, patients with β-thalassemia major were treated with regular blood transfusions and subcutaneous DFO treatment, while patients with β-thalassemia intermedia were only occasionally transfused. Twenty-five out of the 32 patients had had a splenectomy. Seven subjects had a positive family history for respiratory diseases or allergic symptoms; one had a history of allergic bronchial asthma in infancy; 4 were smokers.

Iron status. Serum iron, serum ferritin levels and transferrin saturation were measured every three months using routine tests.

Blood transfusion regimen. The pretransfusion hemoglobin level ranged from 8.0 to 10.1 g/dL (mean±SD). The β-thalassemia major patients received 2-3 units of blood every 2-4 weeks (approximately 20 mL/kg of packed red blood cells).

Desferrioxamine treatment. All patients with β-thalassemia received daily chelation therapy with subcutaneous injection of DFO (20-40 mg/kg/day).

Clinical examination. During the entire study period no patients had any symptoms of acute disease of the respiratory tract; at the time of the study all patients were in a stable condition.

Otorhinolaryngologic assessment. All patients underwent an examination of the upper respiratory tract.

Chest x-ray. All patients had a chest X-ray on entry to the study.

Pulmonary function tests. These were performed using a body plethysmograph. Bacalo *et al.*[4] and Santamaria *et al*.[5] described a significant reduction in the forced expiratory volume in 1 sec. (FEV_1) and forced vital capacity (FVC) following blood transfusion and therefore all tests were performed in the morning, 24 hours before the patient received the planned blood transfusion.

FVC, FEV_1, total lung capacity (TLC) and residual volume (RV) were recorded using a pneumotacograph: the best of three technically acceptable values was selected. Values are reported in liters and as percentages of predicted normal values,[6,7] corrected for body temperature, atmospheric pressure and saturation with water vapor. Restrictive failure was classified as mild when TLC values were between 70-79% of predicted, as moderate between 60-69% of predicted and severe when < 60% of predicted.

Diffusing capacity. The carbon monoxide diffusion capacity of the lung (DL_{CO}) was measured by the single breath method[8,9] and the values obtained were corrected for Hb concentration.[18] We considered values under 80% of predicted as diagnostic of abnormal diffusion capacity.

Blood gases. pO_2 and pCO_2 were determined by arterial blood gas analysis.

Echocardiogram and cardiologic evaluation. Cardiac function was evaluated by ECG and echocardiogram: echocardiographic ejection fraction, calculated from M-mode recordings or two-dimensional M-mode studies, was employed to assess cardiac function.

Statisticsl evaluations. Comparisons with normal values were made using Student's unpaired t-test; results were considered statistically significant when $p < 0.05$; linear regression was used to analyze the joint effects of several variables. Summarized data are presented using correlation coefficients and means ± SD for group data.

Results

Thirty-two patients were evaluated: 19 with β-thalassemia major and 13 with β-thalassemia intermedia.

Upper respiratory tract findings. Of the patients with β-thalassemia major, one had nasal polyposis and one suffered from chronic sinusitis; 7 reported seasonal allergic rhinitis but had no symptoms and were negative when tested for bronchial hyperresponsiveness.

Clinical evaluation. No clinical signs of pulmonary dysfunction or evidence of heart failure were found.

Chest X-ray was normal in 13 patients with β-thalassemia major and in 6 with β-thalassemia intermedia, while in the remaining a reticulo-nodular pattern was described. These findings did not correlate with results of the respiratory function tests: in fact, all the patients with the more severe restriction had a normal chest X-ray.

Arterial oxygen saturation was normal in all patients (mean value 98%).

Table 1 shows the main results of pulmonary function in β-thalassemic patients. Results are expressed as mean ± standard deviation (SD). TLC was below the mean predicted value for age and height in 12 of 19 patients (63.15%) with β-thalassemia major, and in 6 of 13 patients (46.15%) with β-thalassemia intermedia. FVC, FVC_1 and RV were also significantly reduced indicating restrictive lung dysfunction. Of the β-thalassemic major patients, 6 had mild, 3 moderate and 3 severe restrictive disease; in β-thalassemia intermedia patients the restrictive pattern was always mild.

In contrast with previous reports,[2] in our study there was no evidence of an inverse correlation between TLC and age ($r = 0.250$; $p = 0.33$ in β-thalassemia major and $r = –0.527$; $p = 0.07$ in β-thalassemia intermedia), but the age range might have been too limited.

When corrected for hemoglobin concentration, DL_{CO} values approached the lower limits of normal in 6 of subjects with β-thalassemia major (mean value: 24.29±4.94 mL/min/mmHg, p=0.077). The mean

Table 1. Pulmonary function in β–thalassemic patients.

	Observed (L)	Predicted (L)	Percentage (mean±SD)
Thalassemia major			
TLC	3.81±0.93°	5.10±0.77	74.18±13.81
FVC	3.09±0.8°	3.90±0.63	78.26±13.61
FEV_1	2.70±0.68°	3.46±0.56	78.58±12.89
RV	0.93±0.35°	1.29±0.13	71.76±25.08
Thalassemia intermediate			
TLC	4.64±1.10*	5.56±0.86	82.27±11.13
FVC	3.05±0.86°	3.86±0.65	76.92±11.77
FEV_1	2.77±0.77 (NS)	3.25±0.48	80.46±12.55
RV	1.48±0.41 (NS)	1.51±0.25	98.73±28.30

*Statistical difference between observed and predicted values: *significant ($p < 0.05$); °highly significant ($p < 0.01$). NS= non significant.*

serum ferritin levels were 1594±1,800 ng/m^2 (range 510-8,629; normal values: 30-320 ng/mL) in β-thalassemia major and 831±673 (range 120-2,413) in β-thalassemia intermedia patients, respectively. No relationship was found between TLC and serum ferritin levels or cumulative DFO dose (r = –0.167; p=0.522 in β-thalassemia major and r= –0.491; p=0.14 in β-thalassemia intermedia).

Cardiologic findings. No arrhythmia or signs of congestive heart failure or pulmonary hypertension were found. All the enrolled patients had an ejection fraction > 60% (mean value: 67.3±5.54%).

Table 2 shows the main characteristics of patients in terms of pulmonary function and serum ferritin levels expressed as a mean of values over the previous year.

Table 2. Severity of respiratory dysfunction, age and ferritin levels (ng/dL) of patients espressed as mean values.

	Respiratory function	Age	Ferritin level
Thalassemia major			
	Normal	23.4±2.2	1,251±783
	Mild	26±1.4	984±280
	Moderate	22±5.6	4,748±5,487
	Severe	22±1.4	1,162±229
T. intermediate			
	Normal	28.5±6.5	638±602
	Mild	24±4.2	1,657±1,068

Discussion

Several investigators have studied pulmonary function in β-thalassemia patients,[10-12,14,15,19,20] but their results are conflicting, and variably small airway obstruction or a restrictive pattern of lung disease have been described. Table 3 shows the main data reported in literature concerning pulmonary function in β-thalassemic patients.

We evaluated pulmonary function in 32 β-thalassemia patients, by means of spirometry, lung volumes, diffusion capacity and arterial blood gas analysis. A restrictive failure pattern was the predominant observation in β-thalassemia major patients. We found no correlation between the degree of restriction and serum ferritin levels, chelation treatment or number of transfusions.

The reasons for these respiratory alterations may be manifold: foremost, deposition and tissue accumulation of iron may be critical for the development of

Table 3. Main data reported in literature concerning pulmonary function in β-thalassemic patients.

Author	N° of patients	Age	pO_2	Pulmonary function	D_{LCO}
Cooper ,1980 (10)	17	6–18	hypoxemia in 15/17	restriction in 8/17	reduced in 13/15
Keens, 1980 (11)	12	18.4±2.6	hypoxemia in 10 /12	small airway obstruction in 11/12	normal
Hoyt, 1986 (12)	19	10–29	–	small airway obstruction	normal in 16/19
Grant, 1986 (13)	8	14–24	hypoxemia in 5/8	restriction	reduced but increased after transfusion
Fung, 1987 (14)	28		–	mild restriction	normal
Freedman, 1990 (15)	8		–	restriction	–
Grisaru, 1990 (1)	35	8–33	hypoxemia in 85 %	restriction in 24/35 obstruction in 2/35	reduced in 50 %
Lands, 1991 (16)	10	7–23	–	normal	–
Bacalo, 1992 (4)	17	6–17	hypoxemia in 2/17	restriction in 7/17	reduced in 57 %
Luyt , 1993 (3)	15	5–18	hypoxemia in 6/13	restriction	reduced
Factor , 1994 (2)	29	6–40	hypoxemia in 1/29	restriction	reduced in 7/29
Santamaria , 1994 (5)	12	13.4±3.9	increases after transfusion	restriction	increased after transfusion

a restrictive pattern of lung dysfunction in β-thalassemia. Iron deposition could play a central role in promoting tissue damage. Iron deposition in the lung may theoretically be correlated with serum ferritin values or iron deposits in the liver. We did not, however, find relationships between restrictive lung disease and serum ferritin levels, desferrioxamine dose, or liver iron concentration (data not shown). It is well known that serum ferritin, although being a common parameter used for monitoring chelation therapy, does not accurately reflect the total iron burden as documented in different reports.[21]

The relationship between altered pulmonary function tests and iron deposition in the lung remains unclear.

Landing[22] found that some patients had pulmonary hemosiderosis, ferrugination of connective tissue, alveolar septa and blood vessels, and interstitial fibrosis: all these derangements could predispose to the development of restrictive lung disease.

Conversely, Grisaru,[1] examining autopsy specimens of 6 subjects with β-thalassemia major, found normal alveolar septa and only one case of increased hemosiderin deposits; in one other case, small recent thrombi were found in some small branches of the pulmonary arteries.

Cooper[10] evaluated lung autopsy specimens from 8 patients with thalassemia and found no sign of fibrosis.

In an autopsy series, 44% of thalassemia patients had evidence of pulmonary arterial obstruction[23] in spite of the fact that only a limited number had had recurrent chest pain, hypoxemia and right ventricular hypertrophy.

Patients with thalassemia, particularly those with thalassemia intermedia, may suffer recurrent pulmonary thromboembolism because of a hypercoagulable state caused by the high number of circulating nucleated red cells.[24]

The chronic accumulation of interstitial or parenchymal fluid determined by subclinical heart failure due to multiple transfusions, coupled with a damaged myocardium caused by iron deposition, may lead to reduced lung compliance.

Grisaru[1] highlights the occurrence of right ventricular dysfunction and abnormal pulmonary function in thalassemia patients.The patients in our study were specifically selected for having normal cardiac function as assessed by physical examination, ECG and echocardiography; one can therefore speculate that the lung function derangements found in our patient reflect a primary lung pathologic condition.

Lands[16] studied 10 thalassemic subjects pre- and post-diuresis in order to evaluate the role of possible fluid overload in altering pulmonary function: baseline function was normal and no change occurred following diuresis.

Luyt[3] measured free radical production by polymorphonuclear cells to identify a potential relationship with tissue damage in the lungs, but the results failed to indicate any correlation with pulmonary function parameters.

Hepatosplenomegaly may contribute to a lung restrictive pattern by reducing chest wall compliance while increases in vital capacity and expiratory reserve volume are observed in patients following splenectomy.[13] Only 6 patients in our population had mild hepatosplenomegaly, 25 had been splenectomized.

The presence of a respiratory restrictive pattern may also be partially explained by thwarted or insufficient anatomical and functional development of the lung during early infancy:[10] thus a restrictive lung disease could develop not from pulmonary fibrosis but from an aberrant growth process that limits the volume of the peripheral airspaces.

It has been observed[2,13] that in thalassemic patients the severity of restrictive disease increases with age. We did not find such a correlation, but this was probably because of the limited age range of our patients. It is our intention to prolong the follow-up of our study population since we have failed to demonstrate the inverse correlation between TLC and age that has previously been described by other authors.

In conclusion, as hypothesised by Santamaria,[17] lung dysfunction in β-thalassemia may be multifaceted: in fact, the existence of an *a priori* situation is possible which, irrespective of the transfusional regimens, could worsen the consequences of iron deposition.

The data available so far do not allow identification of a single pathophysiological mechanism responsible for pulmonary dysfunction. Our data suggest the need to include periodic lung function testing in the follow-up of all β-thalassemia patients. It should be noted that alterations are present at a young age and may deteriorate into severe respiratory failure.

Contributions and Acknowledgments

GP was the main investigator: she performed the respiratory evaluation and pulmonary functionality tests; UA was responsible for evaluation of the upper repiratory tarct. MDC was responsible for the Thalassemia Center and she selected the patients and took care of the follow-up of the patients; FT was a patient assistant; LA and GF contributed to the design of the study, critically revised the manuscript and gave the final approval for its submission. The order of the authorship was made on the basis of the contributions given to the study. We wish to thank L. Zanaboni and L. Ciceri from the Thalassemia Center for their helpful suggestions.

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Disclosures

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