

Comparison of pulmonary functions of thalassemic and of healthy children

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ABSTRACT

Objectives The aim of this study was to compare some pulmonary functions of thalassemic patients and those of normal children. Factors correlated with lung dysfunction were assessed.

Methods This cross-sectional study compared some pulmonary functions of thalassemic patients with those of healthy children. The study was performed in the Department of Child Health, Cipto Mangunkusumo Hospital, Jakarta, Indonesia. Pre- and post-transfusion hemoglobin levels of the thalassemic subjects were determined. Other data such as chelation therapy and serum ferritin levels were also obtained. Both thalassemic and control subjects underwent routine physical examinations and lung function tests using an electronic spirometer. Spirometry was repeated three times for each subject, and only the best result was recorded.

Results Sixty-three thalassemic patients were enrolled, consisting of 32 male and 31 female subjects. Healthy subjects consisted of 31 males and 31 females. Most thalassemic patients (46/63) were found to have lung function abnormalities. This was significantly different from control subjects, of whom most (39/62) had normal lung function. Restrictive lung function abnormality was the most common (42/63) observation documented. Serum ferritin levels were obtained from 28 male and 29 female thalassemic subjects. There was no correlation between percentage from predicted forced vital capacity and serum ferritin levels, whether in male ($r=0.191$; $P=0.967$) or female ($r=-0.076$, $P=0.695$) thalassemic subjects.

Conclusion Thalassemic patients have significantly lower lung function than healthy children. More thalassemic patients had lung function abnormalities compared to healthy children. Restrictive dysfunction was the most common finding in the thalassemic group. No correlation was found between lung function and serum ferritin levels [Paediatr Indones 2005;45:1-6].

Keywords: pulmonary function, thalassemia, spirometry, serum ferritin level, restrictive lung dysfunction

Thalassemia refers to a heterogeneous group of heritable hypochromic anemias of various degrees of severity;¹⁻⁹ it is considered to be the most prevalent genetic disorder in the world.³ Transfusions of 15-20 ml/kg of packed cells are usually required every 4-5 weeks.⁹ Unless adequate chelating agent is prescribed, hemosiderosis is an unavoidable consequence of long-term transfusion therapy, because each 500 ml of blood delivers to the tissues about 200 mg of iron that cannot be excreted by physiologic means. Besides the heart, liver and pancreas as the target organs most frequently involved, abnormalities of lung mechanics have been reported by almost all studies of patients with thalassemia.¹⁰⁻¹¹

There is no consensus on the nature of lung impairment in thalassemic patients. Most studies found that restrictive dysfunction is the predominant pattern of lung function abnormality in thalassemic patients^{1-2,4-7}, although some others found obstructive lung dysfunction as the major pattern.¹²⁻¹⁵ Furthermore, the relationship between changes in the lung mechanics of transfusion-dependent thalassemic pa-

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tients and iron burden or overload remains unclear. Some studies find a significant inverse correlation between total lung capacity and iron burden¹⁻³ as well as between total lung capacity and age.^{1,2} Others find that neither age⁴ nor iron load^{4,5,8} correlated with pulmonary function. To our knowledge, no data on this issue is available in Indonesia. The aim of this study was to compare the pulmonary function of thalassemic patients to that of normal children. Factors correlated with lung dysfunction, including serum ferritin level, were also assessed.

Methods

This was a cross-sectional study comparing thalassemic patients with healthy children. Patients enrolled in the study were those visiting the Thalassemia Center, Cipto Mangunkusumo Hospital, Jakarta during the period of the study. The study protocol was approved by the Committee of Medical Research Ethics of the Medical School, University of Indonesia. Subjects were patients with either homozygous β -thalassemia or compound hemoglobin E- β thalassemia.

Two calculations were performed to determine sample size. The first was in accordance to the first objective of this study, which was to compare pulmonary function between thalassemic patients and normal children. The primary variable to be investigated in this study was forced vital capacity (FVC), therefore calculation of sample size was based on this variable, using the formula to calculate sample size of two independent groups.¹⁶ With level of significance (α) of 0.05, power of 0.80, standard deviation of two groups of 14%,^{4,5} and clinically important difference of 10%, the sample size was found to be 31. As this study differentiated between male and female subjects, the total sample size was 62 subjects for the thalassemic group and 62 for the control group. The second calculation was based on the objective of evaluating the correlation between serum ferritin level and pulmonary function in thalassemic patients. For this purpose, sample size was determined using the sample size table for correlation coefficient.¹⁶ With a correlation coefficient (r) of 0.6;² level of significance (α) of 0.05; and power of 0.20, the sample size was found to be 19.¹⁶ We decided to comply with the larger sample requirement as determined in the first calculation.

To be enrolled in this study, the thalassemic patients were required to be at least 6 years and not older than 12 years of age. Informed consent had to be obtained from their parents. Patients were recruited if they were clinically stable and had just received their latest regular transfusion to achieve a minimum hemoglobin level of 9 g/dl at the time of the study.

They were excluded if on physical examination they were found to have cardiac dysfunction i.e., cardiac failure, or obstructive lung disorder i.e., asthma.

Data regarding identity, date of birth, and history of illness including the age at which the diagnosis of thalassemia was established and the use of chelation therapy were obtained from parents and medical records. Chelation therapy was considered adequate if it involved intravenous deferoxamine infusions, >3 times a week.¹⁷ When information on chelation therapy from the history was discordant with medical record data, or when medical record data was incomplete, information from the parents will be recorded. Transfusion years were calculated by subtracting current age with age at the time of diagnosis. Routine physical examinations were performed and the results recorded. Data on pre-transfusion hemoglobin (Hb) level and most recent serum ferritin level were also taken. After subjects had their regular transfusion, venous blood samples were taken to attain their post-transfusion Hb level. Only those who achieved a post-transfusion Hb level of 9 g/dl or higher were included. Patients were let to rest for 30 minutes. Each subject then performed lung function tests by means of electronic spirometer AS-7.¹⁸

Control subjects consisted of 6 to 12 year old children attending SDN Pegangsaan 01 elementary school, Jakarta who did not have any sign or symptom of respiratory illness, cardiac failure, or any other significant health problem. Subjects were selected in a random method from this accessible population. History of illness was taken, routine physical examination was performed and the results were recorded. Subjects then performed lung function tests by means of an AS-7 electronic spirometer.

Each subject performed spirometry three times, of which only the best result was recorded.¹⁹ Data recorded during spirometry were forced vital capacity (FVC), one-second forced expiratory volume (FEV₁), ratio of FEV₁ to FVC (FEV₁/FVC), peak expiratory flow (PEF), V₂₅, and V₅₀. All data were expressed as percentage of the predicted normal values according

to age, sex and present height (% predicted). FVC and FEV₁ values of less than 80% of the predicted normal values were classified as abnormal.¹⁶ The means (SD) of these values were calculated.

Spirometry results were categorized as consistent with the normal pattern (normal FVC and FEV₁/FVC ratio), restrictive pattern (reduced FVC, normal or elevated FEV₁/FVC ratio), or obstructive pattern (reduced FEV₁/FVC ratio, normal or reduced FVC).¹⁸⁻²⁰ The results obtained from spirometry were also determined and confirmed by plotting spirometry values to a pentagram, calculating the obstruction index (OI), and generating a flow-volume (F-V) curve. An F-V curve was said to exhibit a restrictive pattern if it was similar in shape with, but smaller than, the normal curve. The curve was considered as showing an obstructive pattern if the portion of the curve after peak flow took on a concave or "scooped out" shape.¹⁸⁻²⁰ Subjects were classified as having normal lung function, restrictive, obstructive, or combined (restrictive and obstructive) pattern lung dysfunction.

Statistical analyses used were Student's t-test for comparing means between the two groups and correlation coefficient for determining the correlation between lung function (FVC) and serum ferritin. The level of significance was taken at P<0.05. Data collected were processed using SPSS 11.0 for Windows.

Results

There were 63 thalassemic patients enrolled in this study, comprising 32 males and 31 females. Healthy

subjects consisted of 31 males and 31 females. The characteristics of subjects are shown in **Table 1**. All thalassemic subjects had sufficient post-transfusional hemoglobin levels. The total amount of transfusion received by each subject could be inferred from transfusion years, as all patients in the Thalassemia Center obtained transfusions regularly every 4 weeks unless they looked extremely pallid or have any other disorder requiring extra transfusion.

Serum ferritin values were available from 28 out of 32 male patients, of whom all had higher values than normal, ranging from 671 to 7992 ng/ml (normal reference value: 30-400 ng/ml). Out of 31 females, serum ferritin values were available from 29, of whom only one had a normal value (151 ng/ml; reference value: 20-300 ng/ml). The other female patients had elevated serum ferritin, ranging from 1095 to 13,807 ng/ml (normal reference value: 13-150 ng/ml).

Among the male thalassemic subjects, none had received adequate chelation therapy. Only two female subjects had received adequate chelation therapy, both of whom had normal lung function values. In most patients, chelation therapy was done only once a month, 1-5 days following transfusion. Patients reported that the sparseness of chelation therapy was because they did not have their own syringe pumps and had to borrow them from the Thalassemia Center.

Spirometry results are reported in **Tables 2** and **3**. On average, FVC and FEV₁ of thalassemic patients were significantly lower than predicted values, whereas FEV₁/FVC and PEF were within normal limits. On individual basis, FVC and FEV₁ were less than 80% of the predicted values in 27 and 21 male patients, respectively and in 20 and 16 female patients, respectively.

TABLE 1. SUBJECTS' CHARACTERISTICS

	Male thalassemia (n=32)	Male control (n=31)	Female thalassemia (n=31)	Female control (n=31)
Age, mean (SD) (years)	9.8 (1.91)	9.1 (2.0)	10.0 (1.76)	9.0 (2.00)
Weight, mean (SD) (kg)	23.0 (4.23)	27.3 (5.83)	23.6 (4.32)	25.5 (6.46)
Height, mean (SD) (cm)	123.6 (8.68)	126.6 (8.73)	121.3 (7.63)	125.0 (9.21)
Post transfusional Hb, mean (SD) (g/dl)	10.8 (1.84)		10.9 (1.28)	
Age at the time of diagnosis, mean (SD) (years)	2.47 (2.92)		2.13 (1.86)	
Transfusion years, mean (SD) (years)	7.4 (2.92)		7.9 (2.29)	
Serum ferritin mean (SD) (ng/ml)	4178.18 (2299.33) (n=26)		4779.26 (3696.47) (n=23)	
Chelation therapy				
- Adequate	0/32		2/31	
- Inadequate	32/32		29/31	

TABLE 2. LUNG FUNCTION TEST VALUES: SEX-SPECIFIC COMPARISON BETWEEN THALASSEMIC AND CONTROL SUBJECTS

	Male thalassemia (n=32)	Male control (n=31)	Significance	Female thalassemia (n=31)	Female control (n=31)	Significance
FVC (% predicted)*	67.7 (12.81)	80.0 (8.73)	P<0.0001**	73.9 (20.56)	83.6 (6.82)	P=0.018**
FEV ₁ (% predicted)*	73.5 (12.60)	86.6 (9.57)	P<0.0001**	81.0 (22.79)	89.8 (8.20)	P=0.050**
FEV ₁ / FVC*	94.9 (6.31)	93.6 (3.31)	P=0.306**	96.6 (3.87)	94.6 (3.95)	P=0.054**
PEF (% predicted)*	99.2 (21.79)	111.5 (13.98)	P=0.010**	130.4 (42.38)	138.2 (27.66)	P=0.396**
V ₅₀ (% predicted)*	81.8 (20.53)	95.2 (17.67)	P=0.007**	101.0 (36.35)	105.9 (26.43)	P=0.548**
V ₂₅ (% predicted)*	86.3 (34.01)	97.6 (24.25)	P=0.129**	82.0 (24.89)	84.1 (21.21)	P=0.716**
Classification						
- Normal	6/32	16/31		11/31	23/31	
- Restrictive	24/32	13/31	P=0.028***	18/31	6/31	P=0.009***
- Obstructive	1/32	2/31		1/31	2/31	
- Combined	1/32			1/31		

* = values are presented as mean (SD) ** = independent t-test *** = chi-square

TABLE 3. LUNG FUNCTION TEST VALUES: ALL THALASSEMIC PATIENTS VS CONTROL SUBJECTS

	Thalassemic patients (n=63)	Control subjects (n=62)	Significance
FVC (% predicted)*	70.8 (17.21)	81.8 (7.97)	P<0.0001**
FEV ₁ (% predicted) *	77.2 (18.57)	88.2 (8.98)	P<0.0001**
FEV ₁ / FVC*	95.7 (5.28)	94.1 (3.65)	P=0.037**
PEF (% predicted) *	114.6 (36.79)	124.9 (25.56)	P=0.061**
V ₅₀ (% predicted) *	91.3 (30.73)	100.6 (22.94)	P=0.271**
V ₂₅ (% predicted) *	84.2 (29.43)	90.9 (23.59)	P=0.127**
Classification			
- Normal	17/63	39/62	
- Restrictive	42/63	19/62	P<0.0001***
- Obstructive	2/63	4/62	
- Combined	2/63		

* = values are presented as mean (SD) ** = independent t test *** = chi-square

Forced vital capacity (FVC) was significantly lower in both male and female thalassemic subjects compared to controls ($P=0.0001$ and 0.018 , respectively). Other lung function measurements in female thalassemic subjects did not differ significantly with female controls. In male thalassemic patients, 1-second forced expiratory volume (FEV₁), peak expiratory flow (PEF) and V₅₀ were significantly lower than in male controls ($P=0.0001$).

Analysis of lung function test results show a significant difference between male patients ($p=0.028$) and female patients ($p=0.009$) with their respective controls. The most common type of lung dysfunction in both male and female patients was the restrictive type. When all subjects were analyzed together regardless of sex (Table 3), significant differences between thalassemic and control subjects were found in FVC (% predicted), FEV₁ (% predicted), FEV₁/FVC, and lung function test results.

Forced vital capacity (% predicted) was not related with age in both male and female thalassemic subjects

($r=0.008$; $P=0.967$ and $r=0.202$; $P=0.277$, respectively). Correlation analysis of transfusion years with forced vital capacity (% predicted) resulted in no significant correlation, both in male ($r=-0.071$; $P=0.701$) and female ($r=-0.074$; $P=0.692$) subjects.

Serum ferritin levels were obtained from 28 male and 29 female thalassemic subjects. There was no correlation found between forced vital capacity (% predicted) and serum ferritin levels both in male ($r=-0.191$; $P=0.967$) and in female ($r=-0.076$, $P=0.695$) subjects.

Discussion

Most thalassemic subjects (46/63) were found to have lung function abnormalities. This was significantly different from control subjects, of whom most (39/62) were found to have normal lung function. This significant difference was present in both males and females. Among the thalassemic subjects, restrictive lung function abnormality was

the most common (42/63) observation documented in this study. Our findings are consistent with those of Carnelli *et al*,¹ Factor *et al*,² Tai *et al*,⁵ Luyt *et al*,⁶ and Filosa *et al*.⁷ What is unique to our study is that it was performed exclusively in children, while those studies mentioned earlier were all performed in both children and adults, with a considerably older mean age. Therefore, our study shows that lung dysfunction in thalassemic patients has occurred since childhood.

The finding of 19 control subjects with restrictive dysfunction drew our attention. Children in the control group live in a highly populated urban slum area. This may add some confounding factors to their lung dysfunction, which was not investigated further in our study. Nevertheless, we exclude the probability of errors in lung function maneuvers, as the tests were performed in optimal condition.

Two thalassemic patients were found to have obstructive lung dysfunction, and two others had combined (restrictive and obstructive) lung abnormalities. In control subjects, there were four children with obstructive lung dysfunction and none with combined disorder. We have attempted to exclude subjects with asthma by careful history taking and physical examination. These findings may be due to limitations in screening, which explain why the obstructive pattern was found in an almost equal proportion of both thalassemic and control subjects. Another possible explanation would be consistent with studies performed by Santamaria *et al*,¹²⁻¹³ Keens *et al*,¹⁴ and Hoyt *et al*¹⁵ which found the obstructive pattern as the most common type of lung dysfunction in thalassemic patients. The mechanism of airway obstruction in thalassemia is unclear. Airway reactivity and a disproportionate growth of the alveolar mass relative to the airways and chest cage have been proposed to be involved in the complex mechanism.¹³

The pathogenesis of restrictive lung dysfunction in thalassemic patients has been associated with hemosiderosis.^{1-2,7} Serum ferritin levels, which reflected iron overload, were abnormal in all but one female thalassemic subject who received regular chelation therapy (5 times a week). However, no correlation was found between serum ferritin levels and any of the lung function values. This finding supported those discovered by Tai *et al*,⁵ and Luyt *et al*,⁶ but contrasted with studies by Carnelli *et al*,¹ Factor *et al*,² and Filosa *et al*.⁷ It is suggested that the duration of iron overload may

be more important than the actual amount of iron provided through transfusions.² Moreover, serum ferritin levels change during the process of chelation, and do not necessarily reflect total body iron stores.² Therefore, a cross-sectional study such as this one, where only the latest serum ferritin level was obtained, lacked the ability to demonstrate the relationship between lung dysfunction and iron overload. A complex mechanism in addition to iron overload has been proposed to play a role in the development of lung dysfunction in thalassemic patients, such as transfusion-dependent chronic fluid accumulation.¹³

Chelation therapy was a confounding factor in this study. Most patients in our study did not receive adequate chelation therapy due to financial reasons. On the other hand, most patients in previous studies had regular and adequate chelation therapy but were still found to have lung dysfunction.^{1-2,5-7,11} This may lead us to question the effectiveness of chelation therapy. Nevertheless, the lung function values observed in our patients were lower than those in other published studies, which may indirectly reflect the benefit of chelation therapy and the role of iron overload.

We conclude that thalassemic patients have significantly lower lung function compared to healthy children, with restrictive dysfunction being the most common type of lung dysfunction in thalassemic patients. We have found no correlation between lung function and serum ferritin values; however, we still suggest that iron overload plays a role in the mechanism of lung abnormalities. No other factor that may contribute to the development of lung dysfunction in thalassemic patients has been found in this study. Further studies concerning the cause and effect of iron overload, or other mechanisms such as chronic fluid accumulation, are needed.

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