Pulmonary Spirometry Parameters in Patients with Sickle Thalassemia and Sickle Cell Disease at Shafa Hospital in Khuzestan Province-Iran

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Abstract

Background

Prevalence of hereditary blood diseases such as sickle cell anemia, sickle thalassemia and thalassemia major are high in Khuzestan province. Sickle cell anemia and beta-thalassemia are predominantly common in Iranian Arabs. Pulmonary complications account for a large proportion of morbidity and mortality in patients with and sickle cell disease. Periodic lung function assessment is recommended to provide a diagnostic clue criterion for physicians.

Objective

The purpose of this study is to assess the spirometry parameters in patients with sickle beta thalassemia and sickle cell disease in south west Iran.

Materials and Methods

Over three months, a total of 35 patients participate in this cross sectional study. Spirometry test was performed on 21 patients with sickle cell disease (12 male, 9 female) and 14 patients with sickle beta thalassemia (7 male, 7 female) aged 6to35 years old. Normal people were matched according to age and sex and were tested as control.

Results

Eighty six percent of sickle cell disease and 57 percent of sickle beta thalassemia had restrictive pattern of lung disease. Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) correlated positively with Hb F level and negatively with Hb S level (P-value<0.001) in sickle cell disease patients (P-value<0.001). Serum ferritin level had a negative effect on FEV_1 and FVC in sickle beta thalassemia patients.

Conclusion

Periodic lung function tests are a useful monitoring test to provide a clinical evaluation profile and have positive correlation with Hb F level.

Key words

Anemia, Sickle Cell, beta-Thalassemia, Spirometry

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Introduction

Sickle cell disease (SCD) and sickle beta-Thalassemia(ST) are a group of hereditary anemia in the world (1-3). According to the last report of the Iranian Ministry of Health nearly 18000 thalassemic major patients are living in Iran (3-4). Khuzestan is a province that is located in the south west Iran with a population of 4.5 million. The total number of thalassemia major patients who are living in this province is about 2000(4). Based on the clinical evidence and hospital records it si estimated that nearly 500 SCD and ST patients live in Khuzestan province.

Polymerization of deoxygenated hemoglobin S is the trigger factor of the disease in SCD and ST (5), which caused by low oxygen tension of venous return and low flow circulation in the microvasculature (6). There are two forms of pulmonary diseases in SCD and ST, acute and chronic. Acute manifestations include the acute chest syndrome (ACS), pulmonary thromboembolism, and hypersensitivity lung disease. Chronic manifestations consist of abnormal pulmonary function, hypoxemia, pulmonary hypertension, and reduced exercise intolerance. Sickle chronic lung disease is a clinical symptoms characterized by dyspnea, exercise intolerance, pleuritic chest pain, and progressive weakening in pulmonary function (7). Most morbidity and mortality of SCD and ST patients are related to pulmonary function level, therefore periodic assessment of pulmonary function in these patients is necessary (8-9). This study was done to evaluate the pulmonary function in patients with SCD and ST in south west Iran.

Materials and Methods

The study protocol was approved by the Research Review Board at Jundishapur University of Medical Sciences and Ahvaz Research Center for Thalassemia and Hemoglobinopathy. The informed consent was obtained from all patients and/or their parents. A questionnaire which included questions about the demographic characteristics, the presenting signs and symptoms, history of transfusion, heart failure, smoking, medication and laboratory parameters were designed.

Twenty one patients with SCD and 14 patients with ST were evaluated and compare with 35 normal volunteers with the same ethnicity and matched age and sex.

Patient with a history of heart disease, smoking, acute infection and hydroxyurea taking were excluded from this study. Inclusion criteria were definite diagnosis of SCD and ST in steady state in patients between 6 to 35 years old.

Pulmonary function tests were done two weeks after the blood transfusion in patients on the regular or occasional transfusion.

Patient age, gender, race, height and weight are recorded before spirometry. Patients should not have eaten large meal three hours before test. Patients should wear loose fitting cloth for test.

Lung volumes and flows were measured in the sitting position, using a closed-circuit spirometer (VG 2000; Mijnhardt BV, Bunnik, the Netherlands).

Restrictive lung disease is defined as a chronic lung disorder that causes a decrease in ability to expand the lung. Pulmonary function test in restrictive pattern demonstrates a decrease in FEV1, FVC and a normalFEV1/FVC ratio. Chronic obstructive lung disease is a general term for a group of conditions in which there is persistent difficulty in expelling (or exhaling) air from the lungs. In obstructive lung disease however, FEV_1 is reduced while FVC remains stable, consequentially depicting a lower FEV_1/FVC ratio.

Statistical Analysis

After collecting data, statistical analysis was performed by SPSS 16.0.2. Differences were considered significant at the level of PV less than 0 .05.

Results:

Twenty one patients with SCD (12 male, 9 female) and 14 patients with ST (7 male, 7 female) in the range of 6-35 years old (mean: 19± 7) and 35 ethnically matched normal volunteers as a control group were tested.

Out of 21 patients with SCD, 18(86%) had a restrictive pattern of lung disease and 3 (14%) had a normal pattern. Of the 14 patients with ST, 8(57%) had a restrictive pattern of lung disease and 6 (43%) had normal pattern (table 1).

Among 35 patients there was an inversely significant correlation between Hb S level with FEV1 and/or FVC in both men and women ($p < 0.001$)(fig1-2), but there was no significant reverse correlation between Hb S level with forced expiratory flow rate at 25% to 75% (FEF25%–75%), and/or FEV1/FVC in them (p: 0.36 and p: 0.46).

There was a significant correlation between Hb F levels and FEV1 and/or FVC values in SCD of both men and women ($P<0.001$) (fig 3-4), but this correlation was not significant between Hb F with FEF at 25-75 and/or FEV1/FVC in them (p: 0.63 and p: 0.43).

There was not found any significant correlation between Hb level and/or serum ferritin with FEV1, FVC, FEF 25-75, FEV1/FVC in SCD patients of both genders (p: 0.36, 0.51, 0.68, 0.75). The reverse significant correlation between serum ferritin with FEV1 and/or FVC was present in ST of both men and women ($p<0.003$) (fig5), but no significant relation was observed between serum ferritin with respect to FEF 25-75 and/or FEV1/FVC (p: 0.13, 0.73).

There was not any significant correlation between Hb level, Hb F and Hb S with FEV1, FVC, FEF 25-75 and FEV1/FVC in ST patients (PV for all more than 0.75).

***Table 1**: Demographic characteristics and spirometry variables of cases and controls.*

Variable	Control group	SCD	ST
Number	35	21	**14**
Age	21.88±8.61	18.71±8.82	**20.07±6.24**
Sex(M/F)	1.19	1.33	**1**
FVC	101.31±13.53	67.14±13.09	**81.79±15.01**
FEV_1	105.42±15.52	65.24±12.65	**79.86±14.18**
FEV/FVC	106.71±9.50	102.52±12.45	**106.43±7.10**
FEF25-75%	85.61±20.38	74.90±22.36	**84.93±34.49**
Hb	13.65±1.7	8.95±1.56	**9.21±0.93**
HbF	1.2±0.6	13.36±8.15	**8.63±5.58**
HbS	-	83.11±9.66	**79.96±9.76**
MCHC	32.34±1.2	33.44±1.62	**29.46±2.98**

Discussion:

Pulmonary complication is a primary cause of morbidity and mortality in SCD and ST patients. The etiology of this complication is multiple (8-9).

Pulmonary complications account for a large proportion of death among adults with sickle cell disease (10-13). According to the cooperative study of sickle cell disease (CSSCD), a prospective multi-center study of 3764 patients, over 20% of patients had fatal pulmonary complications. Pulmonary disease was the most common cause of mortality accounting for 28 % of all deaths (9).

Our study shows that the dominant pattern of lung disease in SCD and ST are restrictive and significantly related to Hb S and Hb F levels in SCD. Serum ferritin values are also correlated in ST patients. High Hb S and low Hb F is a risk factor for death in sickle cell patients and predisposes patients to most of the complications of sickle cell disease such as lung disorders. Hemoglobin F inducer drugs as hydroxyurea (HU) or blood transfusion (simple or exchange)

can reduce morbidity and mortality in this disease. Mean FVC and FEV1 values improved significantly on HU (14-15).

ST patients are compound heterozygotes group whose clinical course is dependent on occasional and regular blood transfusion in these patients iron overload is inevitable. Deposition of iron in lungs may cause pulmonary fibrosis and reduce pulmonary function capacity (16). Our findings confirm this problem. Higher ferritin levels could cause more severe sickling phenotype, but the effect of using iron chelator drugs needs more future study. Eidani et al showed the predominantly restrictive pattern of lung abnormality in thalassemia major patients in south west Iran on pulmonary function testing (17). Piathas et al. showed that the dominant form of pulmonary dysfunction in thalassemia intermediate patients is a restrictive pattern. Spirometry was sufficient to exclude the presence of a restrictive pattern, unless a high degree of clinical suspicion was present (18).

In our study 86% of SCD had a restrictive pattern of pulmonary dysfunction. It is similar to those of Elizabeth et al, who found out that 90% of SCD had pulmonary dysfunction and the most common pattern was a restrictive defect (19).

The restrictive pattern is sequelae of lung injury attributed to repeated episodes of pulmonary damage such as ACS, pneumonia, fat embolization, and pulmonary hypertension. It is associated with a severe clinical course(symptoms) for patients (20).

Studies of lung function in children with SCD have shown various results (21). One study has shown restrictive abnormalities (22); while others have found obstructive abnormalities (20, 23) or no abnormality (24). Present study determined restrictive defects, because most of our patients were adults. These results agree with those of Femi-Pearse et al (25). Most adult patients with sickle cell disease like our patients; develop abnormal pulmonary function characterized by mild restrictive lung disease, abnormal diffusion capacity and radiographic signs of mild pulmonary fibrosis (26-30). Severity of these defects seems to be slightly greater in those patients with pulmonary hypertension (31). Koumbourlis et al suggested that chronic inflammation initially affects the smaller airways. Long-standing inflammation causes lower airway obstruction in early phases, which might lead to fibrosis in later phases (20). This may explain the increased prevalence of restrictive pattern in adults. This will fit with the view held by Sylvester and colleagues who suggest that the restrictive defect becomes obvious with increasing age in children with SCD. Pulmonary hypertension is another complication of SCD and ST patients. The cause of pulmonary hypertension is not completely understood, but chronic hypoxia, hemolysis, and platelet aggregation may play a role. Therefore blood transfusion, blood exchange and hemoglobin F inducing drugs seem to be effective in managing these complications (32, 33).

In our study the rate of pulmonary complication was higher in SCD than ST patients. The ST patients received blood transfusion more than SCD patients. Blood transfusion can relieve hypoxia, haemolysis, and vascular occlusion, but the iron overload is potentially hazardous. Iron deposition in lungs parenchyma could cause pulmonary fibrosis. Iron chelator drugs reduce this complication.

Conclusion

Restrictive lung pattern was common in SCD and ST patients. This pattern correlates positively with HbS levels and inversely with HbF. Periodic lung spirometery is a good recommended test to assess the pulmonary function. Periodic measurement of Hb, Hb F, Hb S and serum ferritin should be considered, because higher HbF levels improves lung function and prevent repeated attacks of acute chest syndrome. Regular or occasional blood transfusion in ST patients or SCD with standard indication also is important.

Acknowledgment

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Conflict of Interest

None declared.

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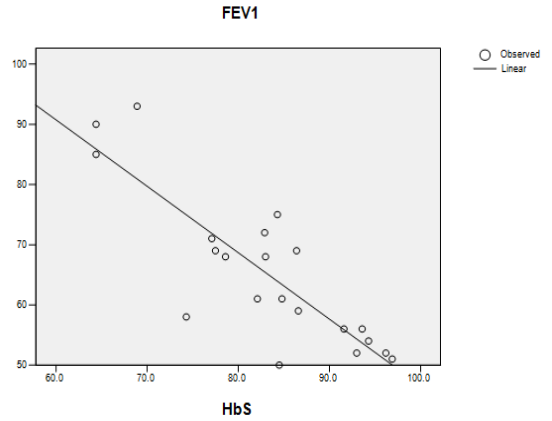

***Fig 1**: Correlation of Hemoglobin S concentrations with FEV1 in Sickle cell (HbSS) patients.*

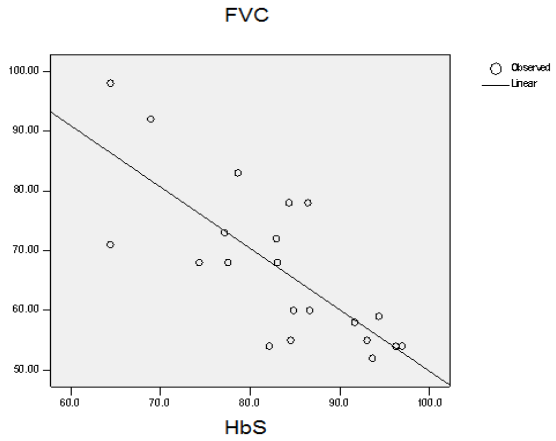

***Fig 2**: Correlation of Hemoglobin S concentrations with FVC in Sickle cell (HbSS) patients.*

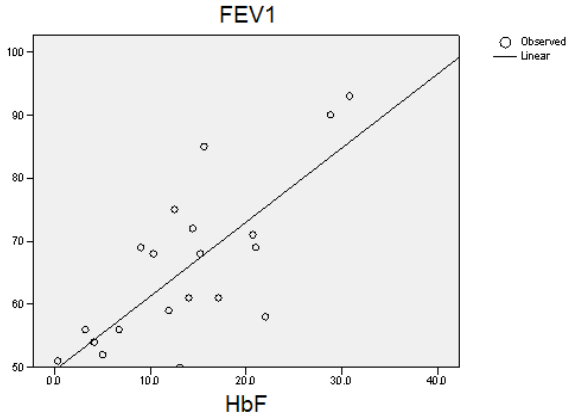

Fig 3: Correlation of Hemoglobin F concentrations with FEV1 in Sickle cell patients.

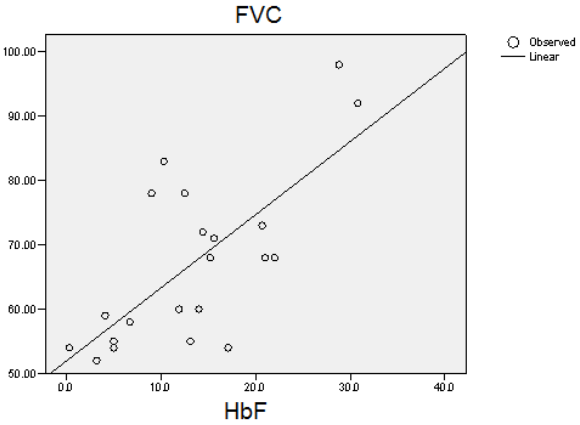

Fig 4: Correlation of Hemoglobin F concentrations with FVC in Sickle cell patients.

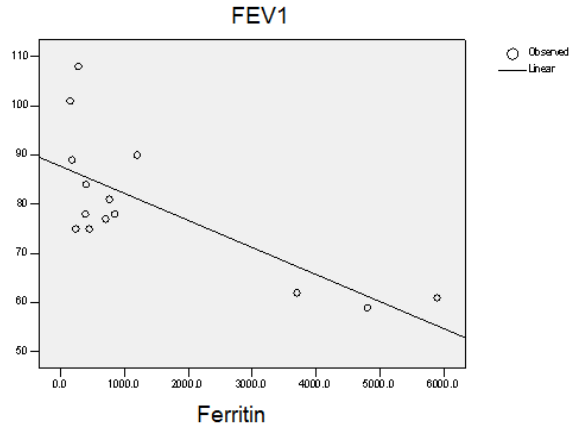

Fig 5: Correlation of serum ferritin concentrations with FEV1 in Sickle thalassemia patients.

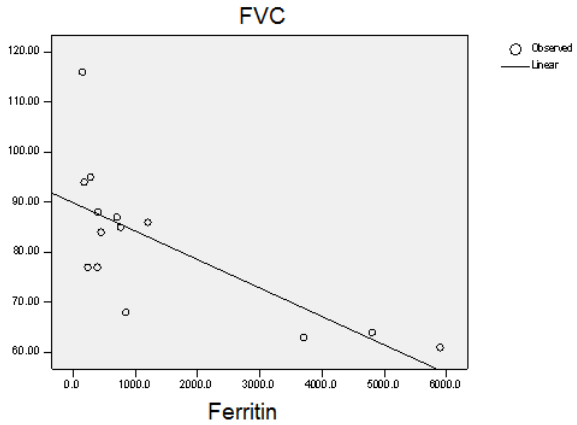

Fig 6: Correlation of serum ferritin concentrations with FVC in Sickle thalassemia patients.