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Pulmonary Function Tests in Children with Sickle Cell Anaemia Between Ages 6 and 18 Years - A Cross-Sectional Study

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Sickle cell Anaemia, Pulmonary Function test, Counselling.

Abstract
BACKGROUND: Sickle cell Anaemia is a common hereditary hemoglobinopathy that affects Pulmonary functions as a consequence of microvasculature obstruction by the sickle cells as well as red blood cell hemolysis. Repeated microvascular obstruction leading to pulmonary hypertension, parenchymal fibrosis, and endothelial dysfunction are probably the main mechanisms for chronic pulmonary diseases in SCA.
METHODS: We have assessed pulmonary function in 62 children of sickle cell anemia between 6 to 18 years of age in a steady-state and its correlation with various important factors like past history of ACS, use of hydroxyurea, number of blood transfusions or the levels of HbF. This study was conducted in a tertiary hospital between Oct 2018 to Dec 2020.
RESULTS: Restrictive pattern of pulmomary function was more common in patients with SCA. HbF was found to have a mild to moderate negative correlation with FEV1/FVC which was statistically significant ($p<0.05$). History of hospital admission was significantly associated with lower FEV1, FVC, and the PEFR, while hydroxyurea use, history of blood transfusion, and history of ACS showed no statistically significant association.
CONCLUSION: SCA may be associated with compromise in the respiratory function in Pediatric patients. Restrictive type changes may be commonly noted in SCA patients which may lead to reduced vital capacity. Hence there is a need for close follow-up and yearly PFT of vulnerable patients.

1. Introduction

Sickle cell disease (SCD) is a common hereditary hemoglobinopathy that is mainly encountered amongst the population of Indian, African, or Arabian origin. Several studies have shown that Cardiopulmonary complications are associated with morbidity in sickle cell disease. Association is found between increased TR jet velocity and decreased FEV1 with increased incidence of mortality in adult patients (1-3). Various events with SCD like Recurrent ACS, asthma, and wheezing predisposes these children to a reduction in Pulmonary function test (4).

The causative factors responsible for ACS are not clear; lung and bone infarction, acute pulmonary sequestration, and infection are among the possible causes of ACS. In children with sickle anemia in steady-state, the main abnormality in pulmonary function is a restrictive pathology, which is found to have multiple characteristics like a slight reduction in total lung capacity, along with an attendant ventilation-perfusion mismatch. This can lead to an alteration in diffusion capacity for carbon monoxide. These aberrations deteriorate with age and are related to increases in pulmonary-artery pressures (5).

The clinical result or impact of SCA is a consequence of microvasculature obstruction by the sickle cells as well as red blood cell hemolysis, leading to multisystemic manifestation. The lungs are impacted in various ways by these pulmonary damages, and reappearance over time may lead to the lungs suffering from chronic interstitial, vascular or parenchymal

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damage which affects pulmonary function. Recent studies have shown 13% hypoxemia in SCA (6).

The static and dynamic pulmonary functions such as FEV1, FVC, MMEFR25-75%, PEFR as well as MVV are lowered in sickle cell disease. Hence, it was decided to evaluate the pulmonary function tests, viz. forced expiratory volume in 1 sec (FEV1), forced vital capacity (FVC), and peak expiratory flow rate (PEFR) in children with sickle cell anemia, between the age group of 6 and 18 years, and in a steady state at a tertiary care hospital in India. It was also decided to assess the correlation of these pulmonary function tests with history of ACS, use of hydroxyurea, number of blood transfusions, or the levels of HbF, to generate important evidence pertaining to the topic.

2. Methodology

We have conducted cross-sectional, observational, and single-arm research to assess respiratory function by measuring pulmonary function tests (FEV1, FVC, PEFR) in 62 children between 6 years and 18 years with SCA in a steady state. We have evaluated the history of acute chest syndrome, history of blood transfusion, hospital admissions, and history of hydroxyurea administration with pulmonary function. Inclusion criteria were all sickle cell Anemia children coming to OPD in steady-state which is a state in SCA patients who are free from sickle cell crisis for at least 4 weeks since the last clinical event, who did not receive a blood transfusion in the last 3 months and free from any infection, pain or other medical illness. Children with sickle cell trait, sickle cell disease other than sickle cell anemia, and any child with SCA with associated chronic medical illness were excluded from the study.

Patient demographics for this study included age, gender, race, and current medications, along with detailed history related to past admissions, blood transfusions, drug history (hydroxyurea), history of ACS, and physical examination were recorded. Anthropometry data was also noted down for the patients. The pulmonary function tests were conducted on the day of the patient enrollment, with the help of the Spirobank G apparatus (Model number: A23-048(0476). Year of manufacture: 2017). The spirometry tests were conducted with the help of a technician, while the readings were noted down by the study investigator. While conducting the spirometry test, the child was asked to breathe in and out normally after tightly pursing the lips over the mouthpiece. Following this, he or she was asked to breathe out forcefully. Wispiro pro was used to analyze the reading. Pulmonary function test parameters like FEV1, FCV, and PEFR were entered in the datasheet.

Statistical analysis was done with the help of statistical software Graphpad InStat.v3.0. Descriptive statistics were used to note down the distribution of patients based on age, anthropometric measurements, gender, patient history details like the use of hydroxyurea, and a total number of transfusions. Quantitative data, viz. the mean PFT values of FEV1, FVC, and PEFR, was presented with the help of Mean and Standard deviation. HbF levels were also analysed. The correlation between the PFTs and HbF levels was assessed using Pearson's correlation coefficient. The mean PFT levels in the sub-group of patients with and without hydroxyurea usage history, with and without transfusion or hospitalization history, and those with or without acute chest syndrome were compared using an unpaired t-test. A P-value of less than 0.05 was considered significant.

3. Result:

Age and sex distribution with anthropometric details.

Our study included 62 patients with SCA with mean age of11.8 ± 3.5 years, with a range of 6 years to 18 years. 53.22 % were females and the remaining 46.78 % were males in the study group.

A. Relationship between respiration pattern and pulmonary function tests: The mean FEV1 was found to be 82.45±16.06 %, and the mean FVC was found to be 82.48± 15.51 % while the mean PEFR was calculated to be 77.74± 22.14 %. The mean FEV1/FVC ratio was calculated to be 97.85 ± 7.76 %. The mean Hb was found to be 9 ±1.68 gm/dl with a range of 5-12 gm/dl (Table 1).

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Table 1: Relationship between respiration pattern and pulmonary function tests

Pattern of respiration	Number of patients (n=62)	Mean FEV1	Mean FVC	Mean PEFR	Mean FEV1/FVC
Normal	38(61.29%)	91.81 ± 9.9	91.92 ±9.36	84.78 ±16.87	97.75 ± 7
Obstructive	4(6.45%)	66.5 ± 7.5	72.75 ±7.65	71.5 ± 21.25	93.5 ±15.08
Restrictive	16(25.8%)	67.93± 14.65	66.25 ± 11.79	62.87 ±26.34	97.5 ± 7.63
Mixed	4(6.45%)	67.5± 6.13	67.5 ± 9.94	76.5 ±26.03	104.5 ± 4.12
P value- one way ANOVA test		<0.01*	<0.01*	<0.01*	0.21

B. Relationship between blood transfusion and pulmonary function tests- 72.58% of the enrolled patients did not have any history of blood transfusions. 9 patients (14.52%) showed a history of one blood transfusion, 6 patients (9.67%) showed a history of two blood transfusions, and 1 patient (1.61%) each showed a history of three or five blood transfusions. The mean FEV1, FVC, PEFR, and FEV1/FVC were all found to be statistically comparable between groups who had a history and who did not have a history of blood transfusion (Table 2).

Table 2: Relationship of blood transfusion and pulmonary function tests.

	Blood transfusion done	Blood transfusion not done	P value
Mean FEV1	82 ± 18.56	82.62 ± 15.24	0.67
Mean FVC	81.52 ±18.19	82.84 ±14.58	0.56
Mean PEFR	75.17 ± 18.33	78.71 ± 23.53	0.35
Mean FEV1/FVC	98.76 ± 7.09	97.51 ± 8.05	0.71

C. Relationship of hospital admissions and pulmonary function tests- 11.29% of enrolled pediatric patients did not show a history of hospital admissions. However, 18 patients each (29.03%) showed a history of 1 or 2 hospital admissions. 12 patients (19.35%) had a history of 3 hospital admissions, 5 patients (8.06%) had a history of 4 hospital admissions and 1 patient (1.61%) each had a history of 5 or 7 hospital admissions. The FEV1, FEVC, and PEFR were significantly lower in the patients who had a history of hospital admission in comparison to those who did not have a hospital admission history. The FEV1/FVC ratio was statistically comparable in the study groups. (Table 3).

Table 3: Relationship between hospital admissions and pulmonary function tests

	History of hospital admission	No History of hospital admission	P value
Mean FEV1	81.23 ± 16.07	92 ± 13.4	<0.01*
Mean FVC	81.41 ± 15.79	90.85 ±10.48	<0.01*
Mean PEFR	76.94 ± 22.61	84 ±18.19	<0.01*
Mean FEV1/FVC	97.79 ± 7.91	98.28 ± 6.99	0.31

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D. Relationship of hydroxyurea use and pulmonary function tests- A total of 69.35% of cases in the study had a history of hydroxyurea usage while the remaining 19 patients (30.65%) had no previous history of hydroxyurea. All the pulmonary function tests (FEV1, FVC, PEFR, and FEV1/FVC ratio) were found to be statistically comparable between the group which had received hydroxyurea and the group which had not received hydroxyurea. (p>0.05) (Table 4).

Table 4: Relationship between hydroxyurea use and pulmonary function tests

	History of hydroxyurea use	No History of hydroxyurea use	P value
Mean FEV1	82 ± 17.61	83.47 ± 12.21	0.36
Mean FVC	81.81 ± 16.27	84 ± 13.92	0.28
Mean PEFR	77.32 ± 24.07	78.68 ± 17.56	0.43
Mean FEV1/FVC	98.29 ± 8.15	96.84± 6.9	0.53

E. Relationship of ACS history and pulmonary function tests - 45 pediatric patients enrolled in the study (72.58%) had no history of acute chest syndrome. 13 patients (20.96%) had a history of 1 ACS episode while 4 patients (6.45%) had a history of 2 ACS episodes. All the pulmonary function tests (FEV1, FVC, PEFR, and FEV1/FVC ratio) were found to be statistically comparable between the group which had a history of ACS and the group which had no ACS history (Table 5).

Table 5: Relationship between ACS history and pulmonary function tests

	History of ACS	No History of ACS	P value
Mean FEV1	82.35 ±16.48	82.48 ± 16.09	0.67
Mean FVC	79.17 ± 15.44	83.73 ± 15.52	0.11
Mean PEFR	75.88 ± 24.81	78.44 ± 21.31	0.29
Mean FEV1/FVC	100.71± 6.28	96.77 ± 8.05	0.16

F: Correlation between HbF and Pulmonary function tests

The mean HbF in the study was calculated to be 7.71 ± 1.32 gm/dl (range: 5.8-8.1 gm/dl). HbF was found to have a mild to moderate negative correlation with FEV1/FVC, and this was found to be a significant finding (correlation coefficient was -0.26) (Table 6).

Table 6: Correlation between HbF and Pulmonary function tests

Correlation assessed	Correlation coefficient (r)	Interpretation	P-value
HbF vs FEV1	-0.18	Mild negative correlation	0.16

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HbF vs FVC	-0.11	Mild negative correlation	0.39
HbF vs PEFR	-0.09	Negligible negative correlation	0.44
HbF vs FEV1/FVC	-0.26	Mild to Moderate negative correlation	**0.04***

4. Discussion

Our study has more females as compared to males, with mean age11.8± 3.5 years. Another study has a mean age was 11 ± 2.3 years and slight female predilection like our study (44.3% males, 55.7% females) (7). Similar findings of female predilection(55.7%) were found in kuti et al (8) with a mean age of 10.1 ± 3 years. In another study by Sylvester et al (9) the mean age was found to be 10 ± 2.4 years, with female participants being 53.13%, identical to that in our study.

The mean FEV1 was found to be 82.45 (±16.06 %), the mean FVC was found to be 82.48 ±15.51 %) and the mean PEFR was calculated to be 77.74 (± 22.14 %). The mean FEV1/FVC ratio was calculated to be 97.85 (± 7.76 %). Based on the % values of these parameters, the respiratory patterns were evaluated in our study. It was found that 38.71% of the enrolled patients suffered from either obstructive, restrictive, or mixed types of respiratory disease. The restrictive type was the most common abnormal respiratory pattern noted, with 25.8% of total cases suffering from the same based on FEV1, FVC, and FEV1/FVC ratio., while the obstructive pattern was noted in 6.45% of cases.

The mean FEV1 was found to be 78.7 (±10.7%), the mean FVC was found to be 85 (±10.6%) and the mean PEFR was calculated to be 79.4 (±13.9%), which were findings almost identical to our study(7). The mean FEV1/FVC ratio was calculated to be 86 (± 5%). A total of 23.4% of enrolled patients suffered from abnormal pulmonary functions in this study, out of which 12% suffered from restrictive while 11% suffered from obstructive lung disease. There have been some other studies that have concluded that restrictive patterns of lung disease may be more common in SCA cases (10,11). In the study by Faleti et al. (12) 6% of the SCA patients suffered from restrictive disease while none suffered from obstructive or mixed lung disease. The FEV1 and PEFR were found to be significantly lower in the sickle cell disease group ($p<0.05$) in comparison to the normal control group. In the study by Kuti et al. (8), the mean FEV1 was found to be 85.9 (± 23%), the mean FVC was found to be 87.7 (± 20.9%), the mean PEFR was calculated to be 75.7 (±13.9%) while the mean FEV1/FVC was calculated to be 89.8 (±14%). The restrictive pattern was commonest in this study at 22.1% which was similar to our study. In the study by Sylvester et al.(9), 9 out of 64 patients suffered from some form of respiratory disease; four children had a restrictive abnormality, three an obstructive abnormality, and two mixed restrictive/obstructive abnormalities.

In our study, the mean HbF in the study was calculated to be 7.71 ± 1.32 gm/dl (range: 5.8- 9 gm/dl). On evaluating the correlation between HbF and pulmonary functions, HbF was found to have a mild to moderate negative correlation with FEV1/FVC, and this was found to be a significant finding ($p<0.05$). This indicates that a rise in HbF was correlated with a fall in FEV1/FVC ratio. The other correlations, i.e., HbF with FEV1, FVC, and PEFR were also found to be negative or inverse but were found to be statistically not significant. In one study, HbF was found to be comparable between the patient subgroup with normal or abnormal PFT (7), while in another study there was a negative correlation between HbF Levels and lung function parameters (13).

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On comparing the PFT findings between subgroups with and without blood transfusion history, mean FEV1, FVC, PEFR, and FEV1/FVC were all found to be statistically compared between groups. This indicated that blood transfusion was not related to significant changes in either FEV1, FVC, PEFR, and FEV1/FVC ratio. These results were comparable with other studies showing no significant difference in PFT between and history of blood transfusion (7,8).

On comparing the PFT findings between subgroups with and without hospitalization history, FEV1, FEVC, and the PEFR were significantly lower in the patients who had a history of hospital admission in comparison to those who did not have hospital admission history. This indicates that hospitalization history, which may be related to some comorbidity or bad medical history (like the previous history of ACS) may impact the pulmonary function, due to which the mentioned pulmonary function in this group was compromised. All the pulmonary function tests (FEV1, FVC, PEFR, and FEV1/FVC ratio) were found to be statistically comparable between the group which had received hydroxyurea and the group which had not received hydroxyurea. Another study showed no significant difference in PFT with the use of hydroxyurea (7). As our study has a small sample size and is conducted in a single-center, the impact of hydroxyurea on pulmonary function, especially in the pediatric population, needs to be explored further.

All the pulmonary function tests (FEV1, FVC, PEFR, and FEV1/FVC ratio) were found to be statistically comparable between the group which had a history of ACS and the group which had no ACS history. This finding was similar to the study by Purohit et al.(14), where PFT parameters of those having a history of ACS were not significantly different than children without a history of ACS. Acute event or active ACS is thought to be responsible for obstructive abnormality. Low peak flow rate and bronchodilator reversibility were demonstrated in some previous studies(15).

5. Conclusion:

SCA may be associated with compromise in the respiratory function in pediatric patients. Restrictive type changes may be commonly noted in SCA patients which may lead to reduced vital capacity. Future studies may help in validating the findings of this study in the Indian population.

6. Recommendations

SCA affects multiple organs and causes progressive damage to multiple organs including the pulmonary system. SCA causes the most restrictive type of changes and this can be identified early by doing pulmonary function tests. Hence, it is recommended that after 4 years of age, annually these patients should be screened for pulmonary function tests. As pulmonary involvement is common and associated with restrictive changes in SCA, there is a reduction in vital capacity. So, daily respiratory exercises should be advised like pranayama and 3-ball incentive spirometer so that it may reduce the functional impairment of the lungs.

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