Acta Neurophysiologica

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Research Article *Volume 4 Issue 8*

Profile of Pulmonary Functions in Pediatric Patients of Sickle Cell Disease

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Received Date: August 07, 2023; **Published Date:** October 25, 2023

Abstract

Background: Pulmonary dysfunctions due to sickle cell disease (SCD) is one of the leading causes of morbidity and mortality in pediatric age group specifically in central India, Chhattisgarh which lies in Sickling belt. Obstructive and restrictive pulmonary changes develop in children with sickle cell disease, but reports conflict as to the type of changes that predominates.

Aim/Objectives: To evaluate pulmonary function tests in pediatric patients of SCD and to understand the pathophysiology & pattern of pulmonary functions. Material and Methods: An analytical cross-sectional study, a total of 75 cases (34 HbSS and 41 HbAS) of SCD aged between 10-14yrs and 45 normal healthy age, sex and ethnic matched control subjects from general population attending the indoor/outdoor in the department of Pediatrics, Pt.J.N.M. Medical college between Nov.2014-Dec.2016. Subjects with cardiac disease, chronic lung disease/disability, acute chest syndrome, subjects with symptoms of chronic respiratory disease and respiratory infection at least two weeks prior were excluded.

Results: Mean FEV1 was significantly lower in heterozygous male as compared to controls. Both mean FEF25%-75% and MVV were significantly less in heterozygous males and females as compared to controls. Both mean FVC & FEV1 were significantly lower in homozygous male as compared to controls. Both mean FEF25%-75% and MVV were significantly less in homozygous males and females as compared to controls.

Conclusion: Pulmonary function is abnormal in children with HbSS and AS. It is likely that abnormal pulmonary function reflects intrinsic lung disease in these patients and the mechanisms are more complex in this population than originally appreciated.

Keywords: Sickle Cell Disease; Electrophoresis; Restrictive and Obstructive Lung Disease

Abbreviations: SCD: Sickle Cell Disease; SCA: Sickle-Cell Anemia; UN: United Nations; WHO: World Health Organization; DNA: Deoxyribonucleic Acid; DLCO: Diffusion Of Carbon Monoxide; ACS: Acute Chest Syndrome; VOC: Vaso-Occlusive Crisis; SCLD: Sickle Cell Chronic Lung Disease; PEF: Peak Expiratory Flow; MVV: Maximum Voluntary Ventilation; PFTS: Pulmonary Function Tests; ATS: American Thoracic Society; ERS: European Respiratory Societies; AS: Heterozygous Patients; SS: Homozygous Patients: FVC: Forced Vital Capacity.

Introduction

Sickle-cell anemia (SCA) is a monogenic, hematological, multi-system disease characterized by repeated episodes of acute disease exacerbations resulting in multi-organ damage.

Globally, it has been projected that the number of individuals with SCA are set to increase dramatically from 305,800 in 2010 to 404,200 by 2050 [1]. Sickle cell anemia (SCA) has recently been recognized as a global public health problem by the UN and WHO [2].

The genetic basis of SCD is the substitution of a single DNA nucleotide in the sixth codon of the gene responsible for the production of β-hemoglobin (thymine for adenine, GAG→GTG). Upon translation, this leads to the substitution of valine for glutamic acid in the sixth position of each β-globin chain of the hemoglobin protein (β6 Glu→Val) [3]. This mutation is a structural variant of normal adult hemoglobin (HbA), which is inherited as a Mendelian trait. Carriers or heterozygotes (AS individuals), inherit an HbS allele from one parent and an HbA allele from the other. These individuals are usually asymptomatic. Homozygotes (SS individuals) who have inherited HbS alleles from both parents suffer from sickle cell anemia, which often leads to acute and chronic complications [2].

Pulmonary function is impaired by the time most patients with SCD reach adulthood. Common abnormalities include obstruction, restriction, and decreased diffusion of carbon monoxide (DLCO), mainly due to repeated lung damage associated with recurrent pulmonary vaso-occlusion. Some lung function parameters may be good indicators of sickle vasculopathy [4]. Involvement of the lungs in sickle cell disease (SCD) is a recognized cause of acute as well as chronic morbidity, which in time becomes detrimental to survival. The on-going vasculopathy in the steady state, recurrent vaso-occlusive crisis (VOC) and acute chest syndrome (ACS) are the major factors contributing to sickle cell chronic lung disease (SCLD), which may eventually lead to cor-pulmonale, in adult patients [5].

The early studies of lung function were performed on adult patients and their findings suggested that SCD was associated with a progressive restrictive lung defect. In 1970, Wall, et al. published the first study of lung function in children with SCD and reported that their lung function was normal. These results were later disputed by Pianosi P, et al. [6] who reported that, like adults, children with SCD had a restrictive pattern. In the first (and to date the only) study of infants, Koumbourlis AC, et al. [7] reported that the majority of infants with SCD had normal lung function and that the only detectable abnormality was lower airway obstruction and not a restrictive lung defect. Koumbourlis AC, et al. [7] confirmed their findings in infants reporting that over 57% of their patients had normal lung function, 35% had obstructive and only 8% had a restrictive pattern.

To date, however, studies of lung function in children with SCD have yielded conflicting results. Only one study has shown restrictive abnormalities, while others have found either obstructive abnormalities or no abnormalities [8]. These discrepancies might be possibly due to over-estimation of the prevalence of the restrictive pattern or under-estimation of the prevalence of the obstructive pattern.

The present study was designed to understand the pathophysiology, pattern of pulmonary functions and to find out if there are demonstrable impairments of pulmonary function by means of spirometry in clinically stable children between 10-14 years of age with sickle cell disease in comparison to age, sex and ethnic matched controls.

Material and Methods

The present study was an analytical cross-sectional study, conducted in the department of Pediatrics and Physiology at Pt. J.N.M. Medical College and associated B.R.A.M. hospital, Raipur, Chhattisgarh after approval by institutional ethics committee.

Inclusion Criteria

Subjects included were patients of sickle cell disease who exhibited clinical and hemodynamic stability and the absence of vasoocclusive crisis for at least one month; attending the indoor and outdoor between November 2014 to December 2016. A total of 75 cases of sickle cell disease between 10-14 years of age were recruited and 45 normal healthy age, sex and ethnic matched control subjects were taken from general population.

Included Subjects were divided into three groups:
Group A- Sickle Cell Disease cases (HbSS): included 34 patients between 10-14 years of age.
Group B- Sickle Cell Trait cases (HbAS): included 41 patients between 10-14 years of age.
Group C- Normal healthy subjects (HbAA): included 45 healthy subjects matched with the cases with respect to age, sex.

Exclusion Criteria

Subjects with history of any cardiac disease, chronic lung disease or disability, acute chest syndrome (ACS), subjects having symptoms strongly suggestive of chronic respiratory disease, and respiratory infection at least two weeks prior to spirometry were excluded from the study.

Methodology

These subjects were evaluated for sickling Sodium meta bisulphide slide test and positive test results were confirmed for trait or disease by performing hemoglobin electrophoresis. Upon agreeing to participate in the study, a written and

informed consent from parents and children for lung function tests were taken; detailed history involving semi-structured questionnaire that obtained sociodemographic data regarding the gender, age, ethnicity/race, marital status, education, occupation, monthly income and medical history of each participant. Physical examination; anthropometric measurement done using standard techniques including Height (centimeters), weight (kg) and body mass index (BMI in kg/m^2) and other necessary laboratory investigations viz. Hemoglobin, fetal hemoglobin, serum bilirubin, and lactate dehydrogenase were determined using standard methods.

Information on the clinical course of the patients, especially regarding the level of hemoglobin, history of ACS, splenic sequestration, VOC, transfusions, asthma and family history of asthma were obtained from their clinical records. Details and diagnoses of previous hospitalizations, and administration of hydroxyurea if the patients had >3 hospitalizations due to severe pain crisis in a year were also taken in consideration.

Lung Function Test

Lung function test was recorded with the Spirometer DATOSPIR-70, a turbine-based device model number-511-700-MU2, manufactured by SIBEL S.A. Barcelona (Spain). Each subject underwent spirometry and forced vital capacity (FVC), forced expiratory volume in 1st second (FEV_1), the ratio FEV_1/FVC, peak expiratory flow (PEF), forced mid expiratory flow at 25–75% of FVC ($FEF_{25\%-75\%}$) and maximum voluntary ventilation (MVV) were recorded. Pulmonary function tests (PFTS) results were interpreted in accordance with the recommendations of the American thoracic society (ATS) and European Respiratory Societies (ERS) [9].

Statistical Analysis

Each parameter was tested for distribution of data. Sociodemographic and Pulmonary functions data are presented as mean ± SD. Paired and un-paired 't' test were used as appropriate for the data by using SPSS software, version 15.

Results

A total of 75 patients of sickle cell anemia (41 HbAS and 34 HbSS) were included after following the exclusion criteria. The diagnosis of sickle cell anemia was confirmed in the laboratory by performing hemoglobin electrophoresis and consent is obtained for study. They were compared with 45 healthy, age and sex matched controls. The period of the study extended from November 2014 to December 2016. The study was approved by institutional ethics committee. All the cases and controls in the study were divided into 3 groups (Homozygous SS, Heterozygous AS and Healthy AA).

The mean age, weight, height, blood pressure, respiratory rate and heart rate for male and females of heterozygous patients (AS) and homozygous patients (SS) was not significantly different to that of control group (Figures 1 & 2).

Table 1 shows the spirometric values of the Heterozygous patients and controls. Mean FEV_1 was significantly lower in heterozygous male patients as compared to controls (p=0.0301*). Both mean $FEF_{25\%-75\%}$ and MVV were significantly less in heterozygous males (p=0.0001*, p=0.0283* respectively) & females (p=0.0118*, p=0.0024* respectively) patients as compared to controls.

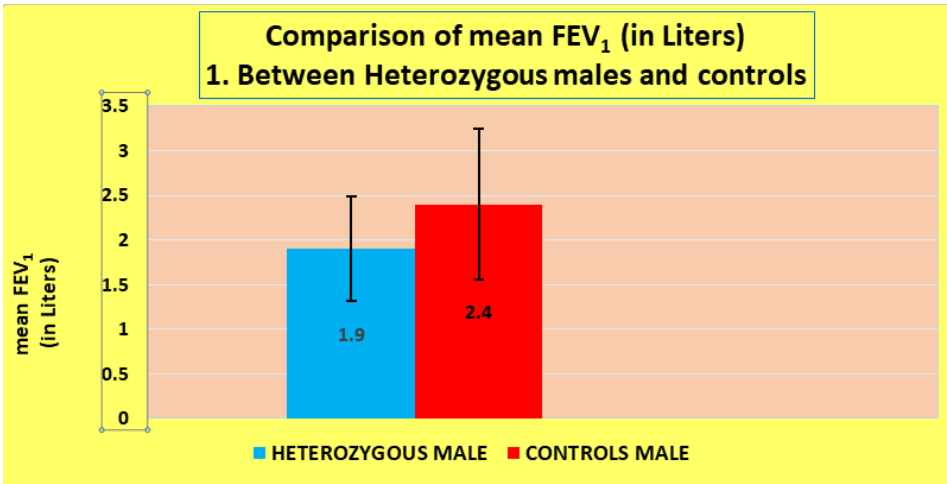

Figure 1: Comparison of mean FEV_1 (in Liters) between Heterozygous males and controls.

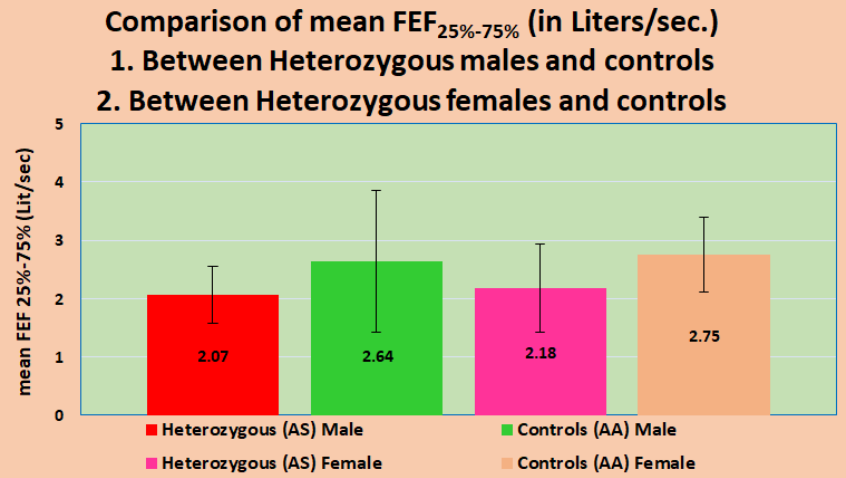

Figure 2: Comparison of mean $FEF_{25\%-75\%}$ (in Liters/sec) A) between Heterozygous males and controls. B) between heterozygous females and controls.

Parameters	Gender	Heterozygous (AS) n=41	Controls (AA) n= 45	p-value (0.05)*
FVC (Lit)	Male	2.50 ± 0.62	2.78 ± 0.93	NS
	Female	2.29 ± 0.55	2.36 ± 0.45	NS
FEV_1 (Lit)	Male	1.90 ± 0.59	2.40 ± 0.85	0.0301*
	Female	1.86 ± 0.47	1.98 ± 0.44	NS
PEF (Lit/sec)	Male	3.01 ± 1.47	3.62 ± 1.35	NS
	Female	3.15 ± 0.76	3.39 ± 0.60	NS
$FEF_{25\%-75\%}$ (Lit/sec)	Male	2.07 ± 0.49	2.64 ± 1.22	0.0001*
	Female	2.18 ± 0.76	2.75 ± 0.64	0.0118*
MVV (Lit/min.)	Male	56.84 ± 17.20	72.09 ± 25.98	0.0283*
	Female	55.85 ± 14.08	69.44 ± 13.04	0.0024*

Table 1: Pulmonary function pattern of the Heterozygous sickle cell patients and controls.
un-paired t-test. data presented as mean ± standard deviation, * p <0.05.

Parameters	Gender	Homozygous (SS) n=34	Controls (AA) n= 45	p-value (0.05)*
FVC (Lit)	Male	2.22 ± 0.54	2.78 ± 0.93	0.0289*
	Female	2.25 ± 0.47	2.36 ± 0.45	NS
FEV_1 (Lit)	Male	1.82 ± 0.46	2.40 ± 0.85	0.0129*
	Female	1.76 ± 0.36	1.98 ± 0.44	NS
PEF (Lit/sec)	Male	2.85 ± 1.15	3.62 ± 1.35	NS
	Female	2.97 ± 0.67	3.39 ± 0.60	NS
$FEF_{25\%-75\%}$ (Lit/sec)	Male	2.10 ± 0.50	2.64 ± 1.22	0.0001*
	Female	2.08 ± 0.55	2.75 ± 0.64	0.0018*
MVV (Lit/min.)	Male	54.53 ± 13.83	72.09 ± 25.98	0.0134*
	Female	52.67 ± 9.92	69.44 ± 13.04	0.0001*

Table 2: Pulmonary function pattern of the Homozygous sickle cell patients and controls.
un-paired t-test. data presented as mean ± standard deviation, * p <0.05.

Table 2 shows the spirometric values of the Homozygous patients and controls. Both mean FVC & FEV_1 were significantly lower in homozygous male patients as compared to controls (p=0.0289*, p=0.0129* respectively).

Both mean $FEF_{25\%-75\%}$ and MVV were significantly less in homozygous males (p=0.0001*, p=0.0134* respectively) & females (p=0.0018*, p=0.0001* respectively) patients as compared to controls.

The pulmonary function profile of the Homozygous was not significantly different from heterozygous patients.

Discussion

Present study has been done in Chhattisgarh State which lies in the sickling belt [10] of India. To assess the lung functions, its impairment and to understand the pathophysiology of pulmonary dysfunction in pediatric SCD patients, spirometric parameters (FVC, FEV_1, PEF, $FEF_{25\%-75\%}$ and MVV) were taken into consideration. The limitation of the study was larger sample should be taken along with assessment of pulmonary hypertension. Sickle Cell Disease can affect many body systems, including the respiratory systems [11], which can impair lung function and functional capacity. Several studies on pulmonary functions in children with SCD shows conflicting results so far (Figures 3-5).

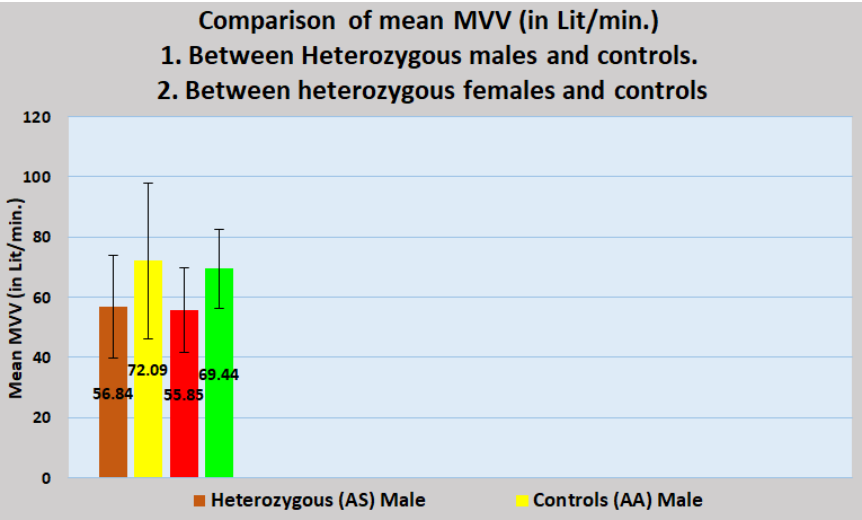

Figure 3: Comparison of mean MVV (in Lit/min) a) between Heterozygous males and controls and b) between Heterozygous females and controls.

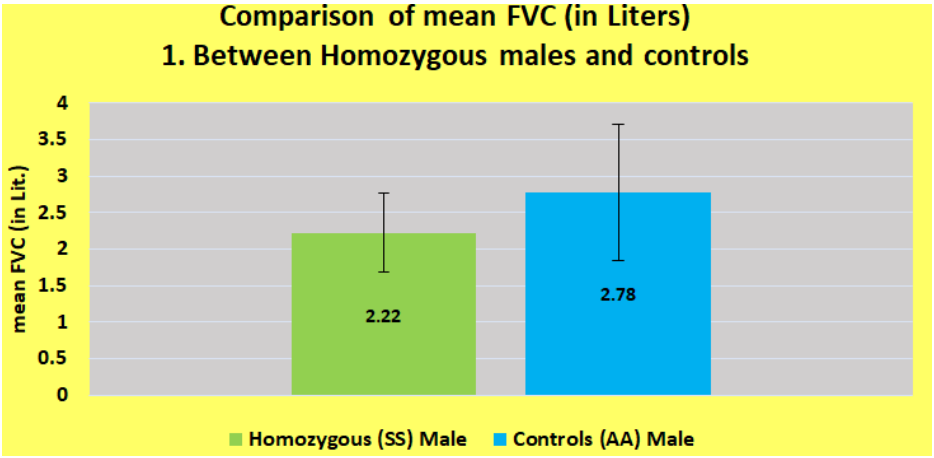

Figure 4: Comparison of mean FVC (in Liters) between Homozygous males and controls.

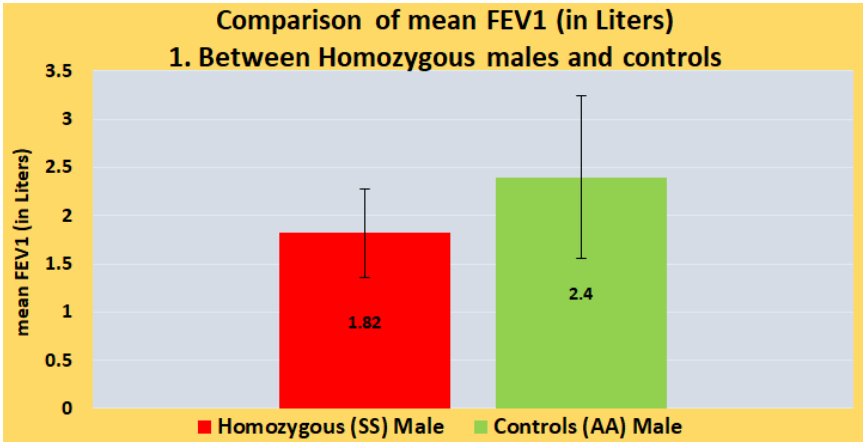

Figure 5: Comparison of mean FEV_1 (in Liters) between Homozygous males and controls.

Pianosi P, et al. [6] in their study in 37 children with sickle cell anemia and 22 control subjects, concluded that children with SCD, particularly those with HbSS, have lower static and dynamic lung volumes and flow rates than control subjects. Prior episodes of ACS do not appear to be associated with PFT abnormalities (Figure 6).

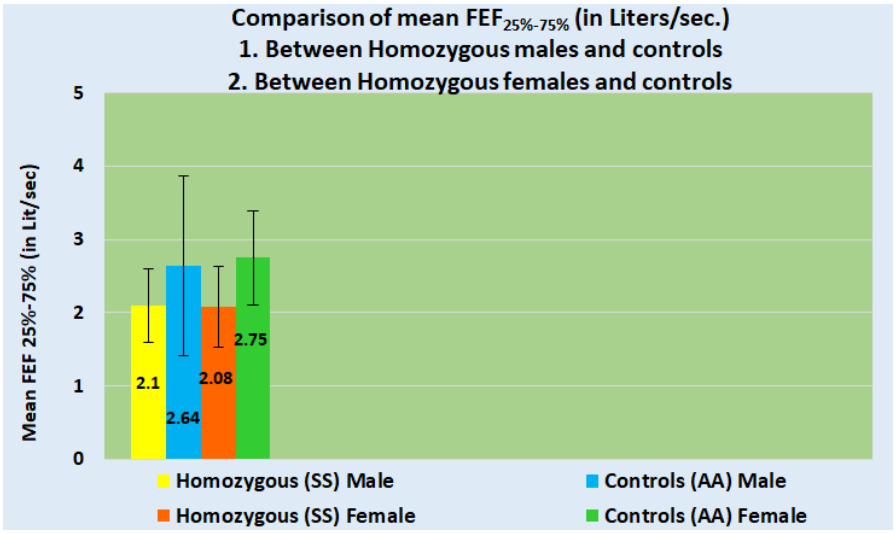

Figure 6: Comparison of mean $FEV_{25\%-75\%}$ (in Liters) a) between Heterozygous males and controls and b) between Heterozygous females and controls.

Sylvester KP, et al. [8] in their study in 64 children with SCD aged 5-16 years and 64 ethnic matched controls, found that the children with SCD had lower FRCHe (p=0.04), FEV_1 (p=0.0008), FVC (p=0.001) and PEF (p=0.0004), but their FEV_1/FVC ratios were not significantly different from those of the controls (Figures 5 & 6). Restrictive and/or obstructive abnormalities were only found in children over 10 years of age.

Hijazi Z, et al. [5] in their study in 55 Kuwaiti children, aged 6-18 years, found an early restrictive pattern, especially in the SS group. Although FEV_1/FVC ratio was similar to that in the control groups, mean FVC and VC values were significantly lower (Figure 7). There was a poor correlation of these values with respect to age. Although patients with frequent vaso-occlusive crisis had lower PFT parameters, the differences were not significant in comparison to those with infrequent crisis.

Arteta M, et al. [12] in their study in 146 children aged 7-20 years found, that the abnormal pulmonary function was predominantly obstructive and is related to both a history of asthma or wheezing and a marker of hemolysis (lactate dehydrogenase).

Willen SM, et al. [13] concluded in their study that, age is a predictor of a small decrease in lung function in children with SCD i.e., $FEV_{1\%}$ predicted declines by 0.3% for every additional year of age (95% CI - 0.56 to - 0.05, p= 0.020). Sex, asthma history, hemoglobin, reticulocyte count, white blood cell count, incidence rate of severe acute pain and ACS episodes and hydroxyurea therapy were not associated with a decline in $FEV_{1\%}$ predicted.

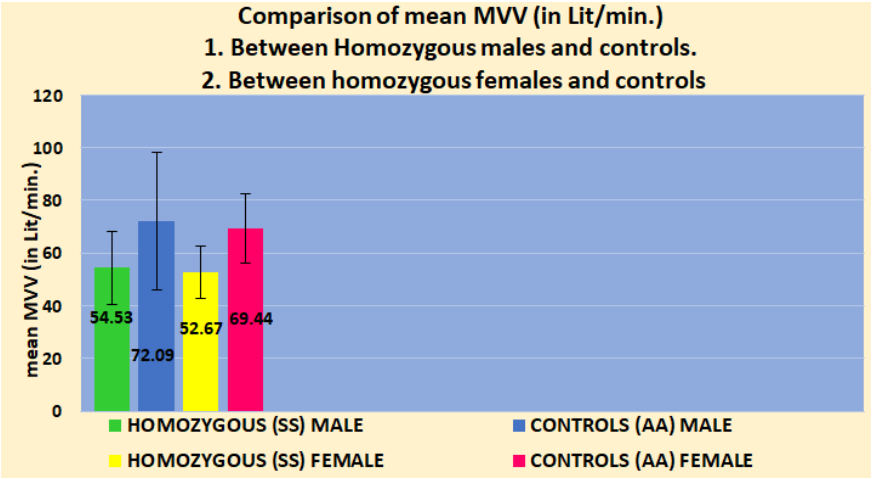

Figure 7: Comparison of mean MVV (in Liters) a) between Heterozygous males and controls and b) between Heterozygous females and controls.

Arigliani M, et al. [14] a total of 112 patients and 377 controls aged between 6-18 years were included. 26% of patients with SCA had spirometry findings suggestive of a restrictive pattern and 41% had a FEV_1 z-score <5th percentile. Malnutrition, increasing age and female sex were all associated with increased risk of a restrictive spirometry pattern.

Biltagi MA, et al. [4] in their study in 139 bahrainian children / adolescents with SCD and 123 healthy controls, found significantly lower FEV_1, FVC, FEV_1/FVC, TLC, DLCO, and DLCOc (ie, hemoglobin corrected DLCO) than in the control group. PFTs revealed significant negative correlations with age, number of ACS events, and sputum IL-6 levels.

In our study, spirometric values of mean FVC, FEV_1, $FEF_{25\%-75\%}$ and MVV were significantly lower in heterozygous and homozygous SCD male patients as compared to control groups whereas mean $FEF_{25\%-75\%}$ and MVV were significantly lower in heterozygous and homozygous SCD female patients as compared to control groups. Forced vital capacity (FVC) represents by lung dimension, compliance and respiratory muscle power whereas PEFR is determined by alveolar caliber, alveolar elastic recoil and respiratory muscle efforts [6]. So, it may represent the early changes in the pulmonary functions in our patient population. There is no significant difference between the heterozygous and homozygous patients in either gender.

All the spirometric values are not significantly different between the groups can be explained with earlier studies which reported normal lung volumes and expiratory flows in children with SCD when compared with those of an appropriate control group as the mean age of our patient group was 13.33 years. Apart, studies reported that lung function abnormalities become more severe as age advances. Studies reported that as the disease advances there was deterioration of pulmonary functions was a prime contributor to mortality in SCD patients. Progressive decline in pulmonary function parameters can be explained from changes in lung compliance and microvascular occlusion developed due to repeated infections, thromboembolic episodes and severity of the attacks [15]. Interstitial lung disease, which is characterized by vascular remodeling and interstitial fibrosis, is a frequent complication of sickle cell anemia and further leads to restrictive, obstructive or mixed pattern of lung disease. Further studies are required to evaluate the effect of SCD on pattern of lung disease in pediatric population.

Conclusion

Pulmonary function is abnormal in children with Hb-SS & AS. It is likely that abnormal pulmonary function reflects intrinsic lung disease in these patients and the mechanisms are more complex in this population than originally appreciated. Greater understanding of the diagnostic utility of pulmonary function testing in this population is paramount as it could lead to a more comprehensive appraisal of the mechanisms responsible for pulmonary complications. Thus, further

more refined longitudinal studies are needed to establish correlation of pulmonary function impairment in children of sickle cell disease with respect to age and duration of illness.

Strategies and Recommendations for Future

Pulmonary function testing turns out be a mainstay; thus, it should be routinely performed in children with Sickle cell disease for the earlier detection of lung abnormalities; and thus, reducing the disease burden and improving healthcare. In children, especially with obstructive pattern of pulmonary dysfunction, possible efforts should be implemented to control the degree of hemolysis and painful crises by prescription of hydroxyurea or other disease modifying treatments.

Acknowledgement

We express our appreciation to Department of Biostatistics for guidance in statistical analysis of the data.

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