Pulmonary function indices in children with sickle cell anemia in Enugu, south-east Nigeria

Kingley I. Achigbu, MBBS, FWACP, Odutola I. Odetunde, MBBS, FWACP; Josephat M. Chinawa, MBBS, FMCPaed, Eherechukwu O. Achigbu, MBBS, FWACS, Anthony N. Ikefuna, MBBS, FMCPaed, Ifeoma J. Emodi, FMCPaed, FWACP; Bede C. Ibe, FMCPaed, FWACP.

ABSTRACT

Objectives: To determine the pulmonary function indices of children with sickle cell anemia (SCA) attending the pediatric sickle cell clinic at the University of Nigeria Teaching Hospital, Enugu, south-east Nigeria and to compare these indices with the results obtained from other regions.

Methods: A case control study of lung function in children with SCA aged 6–20 years. The study was carried out in the University of Nigeria/University of Nigeria Teaching Hospital, Enugu State, Nigeria between October 2014 and January 2015. Measurements of the peak expiratory flow rate, forced vital capacity (FVC), and forced expiratory volume in one second (FEV1) were evaluated.

Results: A total of 80 subjects were recruited into the study, comprising 40 homozygous HbSS (hemoglobin SS) patients and an equal number of controls. Children with SCA had statistically lower values of FEV1 (1.6±0.52), FVC (1.76±0.95), and peak expiratory flow rate (PEFR) (309.00±82.64) when compared with normal hemoglobin genotype FEV1 (12.01±0.53), FVC (12.12±0.54), and PEFR (364.10±87.85). The mean FVC, FEV1/FVC, and PEFR were also higher in the male control group compared with the HbSS male group, but these differences were not statistically significant. Female controls had significantly larger FEV1, FVC, and PEFR values compared with the HbSS females.

Conclusion: The lung function indices were significantly lower in children and adolescents with SCA compared with the matched controls with a hemoglobin genotype AA.
Sickle cell anemia (SCA) is a genetic hematological disorder characterized by red blood cells that assume an abnormal, rigid, sickle shape. This hereditary disorder contributes the equivalent of 3.4% mortality in children aged <5 years worldwide or 6.4% in Africa. The prevalence of SCA in Nigeria ranges from 0.4-3%. Approximately 85% of sickle cell disorders and >70% of all affected births occur in Africa. It is worth noting that at least 5.2% of the world population carry a significant trait. The clinical consequence of SCA results from obstruction of the microvasculature by the sickle cells and red blood cell hemolysis, which causes multi-systemic manifestation. The lungs are affected in a variety of ways by these pulmonary insults, and recurrence overtime may leave the lungs with chronic interstitial, parenchymal, or vascular damage that compromises pulmonary function. It has been documented that the prevalence of hypoxemia among SCA children was 13%. This prevalence was attributable to the chronic anemic state, micro vascular occlusion of the circulation by sickle hemoglobin, and constant perturbation of the endothelial membrane, and consequent elaboration of endothelial molecules, which are commonly seen among SCA children, especially those with various types of vaso-occlusive episodes. This is defined as bone and joint pain or multiple sites of pain needing analgesics or hospitalization. Acute and chronic pulmonary complications occur frequently in patients with SCA, and contribute to morbidity and mortality later in life. Although the pathogenesis of chronic pulmonary disease in sickle cell disease (SCD) has not been clearly defined, recurrent microvascular obstruction resulting in the development of pulmonary hypertension, endothelial dysfunction, and parenchymal fibrosis are probably the primary mechanisms. There is increasing evidence that repeated episodes of acute chest syndrome (ACS) may cause permanent damage to the pulmonary parenchyma and vasculature. Repeated attacks of ACS are a major risk factor for the development of sickle cell chronic lung disease. Studies of lung function in SCD have also demonstrated a restrictive defect, while a reduction in the total lung capacity (TLC) of 50% has been reported in advanced forms. Acute chest syndrome refers to a spectrum of pulmonary pathology having in common, chest pain, fever, dyspnea with abnormal clinical, and radiologic chest signs as well as leucocytosis. It is the most common cause of death in children with sickle cell anemia over 10 years of age. The etiology of ACS is not clear, lung and bone infarction, infection, and acute pulmonary sequestration, among other possible causes have been proposed. In children with sickle anemia in steady state, the major abnormality in pulmonary function is a restrictive pathology, characterized by a slight decrease in total lung capacity, with attendant ventilation perfusion mismatch. This can cause a defect in diffusion capacity for carbon monoxide. Whereas some studies have documented impaired lung function in SCA (hemoglobin SS) patients, previous studies reported what appears to be contrasting findings when the lung function in children with SCA and those of healthy controls with normal hemoglobin genotype were compared. It is therefore necessary that ventilatory function studies be undertaken in this part of the world to see if there is any difference with known values in other part of the world. In this study, we determine the impact of SCA on the pulmonary function indices in patients attending the pediatric sickle cell clinic at the University of Nigeria Teaching Hospital (UNTH) Enugu, south-east Nigeria and compare it with matched controls and other studies. Many studies have described and assessed the pattern of pulmonary function in SCD from childhood to adulthood, but much is not known on this topic in South Eastern Nigeria. Most of the original studies are from western Nigeria. This study could therefore corroborate or refute regional or ethnic differences in lung function in children with SCD. The study hypothesis seeks to answer the following questions? Do children with SCA attending UNTH Enugu present with any alteration in lung function? If they do, is there any gender and age difference? Are these lung volume findings similar to that obtained from other region?

Methods. Study area. This study was carried out in UNTH, Enugu, south-east Nigeria. The hospital is a referral center for various health facilities in Enugu state and surrounding area. Enugu has a population of 3.5 million people according to the National population census.

Study population. These were patients with hemoglobin genotype HbSS attending the pediatric sickle cell clinic at UNTH, who fulfilled the criteria for inclusion into the study. The inclusion criteria include subjects with age between 6-20 years at last birthday. Willingness to participate fully with consent obtained from the patient and parents/guardian. The HbSS patients must be in ‘stable state,’ defined as a state of

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health in which they were free from pain, crises or acute illness within the period of study, namely from the stage of recruitment until the measurement of lung. Subjects with the presence of spinal deformity or any acute or chronic cardio-respiratory disease, which may affect the lung function indices, those with positive history of cigarette smoking among subjects, and controls or other members of their household were excluded from the study. The controls comprised healthy children with hemoglobin genotype HbAA matched for age, gender, and height randomly selected from primary and post primary schools within Enugu metropolis.

**Sample size determination.** A minimum sample size that was representative of the study population was determined using the formula:

\[
\frac{n_f}{n} = 1 + \frac{n}{N}
\]

Wherein \( n_f = \text{definite number of patients; } N = 447 \) (yearly attendance at sickle cell clinic of patients aged 6-20 years); \( z = 1.96 \), critical value at the level of significance (95% confidence interval); \( p = 1.6\% \) prevalence of SCA with an attribute from a previous study at the University of Nigeria Teaching Hospital Enugu; \( d = 0.05 \) (tolerable error). Substituting the above values:

\[
\frac{n}{n_f} = 1.962 \times 0.016 \times (1-0.016) = 0.05^2
\]

Wherein \( n = 24 \), therefore,

\[
\frac{n_f}{n} = \frac{24}{1 + \frac{24}{447}} = 23
\]

This yielded a minimum sample size of 23. To enhance the accuracy of the study results, a sample size of 40 was adopted.

**Ethical consideration and consent.** Ethical clearance for the study was obtained from the Research and Ethical Committee of the UNTH and the Post Primary Schools Management Board, as well as from the Headmasters/ mistresses, and principals of the selected primary and secondary schools whose pupils/students were expected to participate in the study. Informed written consent was obtained from the parents or guardians as appropriate prior to the recruitment of their children or wards into the study. Verbal consent was also obtained from each of the study participants.

**Study design.** A case control study of lung function was conducted in Enugu metropolis. The study was carried out between October 2014 and January 2015. For the controls, the selection process was by multistage sampling. All the post-primary schools selected were government institutions, which have a fair representation of students from all social strata. All the schools selected were visited by the researchers. In each school, 2 streams of each class were randomly selected by simple ballot. In each of the selected streams the students or pupils as appropriate were first stratified according to age, gender, and height. This study was conducted according to the principles of the Helsinki Declaration.

**Pilot study.** A pilot investigation was undertaken in a group of 10 sickle cell (HbSS) patients, and an equal number of healthy controls with genotype HbAA who were subsequently excluded from the main study.

**Pulmonary function tests.** Measurements of the peak expiratory flow rate were taken using a single mini Wright peak flow meter (Airmed, Clement Clarke International Limited Harlow, England, UK). The instrument was calibrated from the factory to a maximum PEFR of 800 litres per minute (l/min). Measurements of the forced vital capacity (FVC) and the forced expiratory volume in one second (FEV1) were taken using an automated single breath vitalograph (Spirovit-SP-1, Schiller-AG, AH Gasse 68, Post Fach, 6340 Barr, Switzerland). Before the commencement of the study, the researchers were trained in the use of all equipment for the present study by the Chief Respiratory Technician connected to the respiratory laboratory at UNTH. Upon completion of the training, the researchers and the Chief Respiratory Technician independently evaluated the FVC, FEV1, and PEFR on the 7 subjects randomly selected from the children’s outpatient clinic. The results obtained by the 2 observers were subjected to statistical analysis using the student t-test. There were no statistically significant difference between the results obtained by the 2 observers. The procedure involved taking as deep a breath as possible, and then applying their lips firmly around the mouthpiece to avoid any air leaks. Thereafter, the subject then breathed out as quickly and as forcibly as possible into the peak flow meter. Recordings were made without nasal clips. After each subject had became familiar with the technique; the procedure was repeated 3 times, and the best results were recorded. For the spirometry, the same procedure was repeated. After a rest of approximately 5 minutes, the subjects after taking a deep a breath as possible
applied their lips tightly to the mouth piece of the spirometer to avoid any air leaks. They were instructed to blow into the mouth piece as rapidly and completely as possible until they were told to stop. Weight in kilograms scale (Deteco scales Inc. Brooklyn, New York, USA) sensitivity 0.5kg, standing height in centimeters (cm) (stadiometer CMS weighing equipment of 17 Campdem Road, London, NW1, UK) were also taken. The social classes of the subjects were determined using the mean of father’s occupation and mother’s education. Socio-economic index scores were awarded to each child using the method recommended. Children with SCA who attended the sickle cell clinic or presented to the Children Emergency ward and fulfilled the inclusion criteria were consecutively recruited into the study while the selection process of the controls was through multistage sampling.

**Data analysis.** All data were coded, entered, and then analyzed using the Statistical Package for Social Sciences program (SPSS Inc., Chicago, IL, USA), version 17. Results were presented in cross tabulation and tables. Data presentation was with tables and graphs. The means, standard deviation (SD), and range of all variables and parameters recorded for the study population were calculated.

For variables such as PEFR, FEV1, and FVC, the student t-test was used to determine statistically significant differences between the mean values in the SS patients and controls. The chi-square test was used to compare the variables such as the age and gender and socio-economic distribution of the SS patients and controls. A $p$-value of <0.05 was considered significant.

**Results.** A total of 80 subjects were recruited into the study, comprising 40 HbSS patients and an equal number of controls (healthy children of the same age, gender, and height). The distribution of the study population according to age and gender as well as the distribution of the HbSS patients and controls according to socio-economic groups is shown in Table 1.

Table 2 showed that children with SCA had statistically lower values of FEV1, FVC, and PEFR when compared with those with normal hemoglobin genotype FEV1, FVC, and PEFR. The mean FVC, FEV1/FVC, and PEFR were also higher in the male controls compared to the HbSS males, but these differences were not statistically significant. Female controls had significantly larger FEV1, FVC and PEFR compared to the SS females ($p=0.01$). Table 3 illustrates that the FEV1 increased consistently with age in both the HbSS patients and controls. The controls had higher FEV1 in all the age groups when compared with the HbSS population, but this value is significant among those whose age falls between 6-10 years (Table 4).

The FVC increased consistently with age in both the HbSS patients and controls. The controls had higher values of FVC compared with the HbSS patients in all age groups. These differences in FVC values were not statistically significant (Table 5). The PEFR increased consistently with age in both the HbSS patients and controls. The controls had comparable values of PEFR with the HbSS patients up to 10 years of age. The PEFR in the controls was higher than PEFR in the HbSS patients at all ages, but became significantly higher from 11-20 years of age ($p=0.007$, $p=0.024$)

### Table 1 - Distribution of the study population according to age and gender as well as the distribution of the HbSS patients and controls according to socio-economic groups.

| Variables               | Male HbSS | Control | $P$-value | Female HbSS | Control | $P$-value | Total HbSS | Control | $P$-value |
|-------------------------|-----------|---------|-----------|-------------|---------|-----------|------------|---------|-----------|
| **Age group (last birthday)** |           |         |           |             |         |           |            |         |           |
| 6-10                    | 4 (20)    | 4 (20)  | 0.926     | 3 (15)      | 3 (15)  | 1.000     | 7 (17.5)  | 7 (17.5)| 0.964     |
| 11-15                   | 11 (55)   | 12 (60) |           | 12 (60)     | 12 (60) |           | 23 (57.5) | 24 (60.0)|           |
| 16-20                   | 5 (25)    | 4 (20)  |           | 5 (25)      | 5 (25)  |           | 10 (25.0) | 9 (22.5)|           |
| Total                   | 20 (100)  | 20 (100)|           | 20 (100)    | 20 (100)|           | 40 (100.0)| 40 (100.0)|           |
| **Socio-economic level**|           |         |           |             |         |           |            |         |           |
| **Upper class**         |           |         |           |             |         |           |            |         |           |
| I                       | 1 (2.5)   | 1 (2.5) | 0.711     |             |         |           |            |         |           |
| II                      | 4 (10.0)  | 6 (15.0)|           |             |         |           |            |         |           |
| **Middle class**        |           |         |           |             |         |           |            |         |           |
| III                     | 11 (27.5) | 10 (25.0)|           |             |         |           |            |         |           |
| **Lower class**         |           |         |           |             |         |           |            |         |           |
| IV                      | 22 (55.0) | 18 (45.0)|           |             |         |           |            |         |           |
| V                       | 2 (5.0)   | 5 (12.5)|           |             |         |           |            |         |           |
| Total                   | 40 (100.0)| 40 (100.0)|           |             |         |           |            |         |           |

Data are presented as number and percentages (%). HbSS - hemoglobin SS. “The social classes of the subjects were determined using the mean of father’s occupation and mother’s education. Socio-economic index scores were awarded to each child using the method recommended.”

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(Table 6). When the observed mean FEV1 of controls in the present study was compared with values predicted from previous studies\(^{18,19}\) at provided heights in both males and females, there was no statistically significant difference between FEV1 observed in the present study and those predicted by the 2 previous studies.\(^{18-20}\)

**Discussion.** The mean FEV1, FVC, and PEFR were all significantly higher in the control group compared with the HbSS patients, while comparable values of FEV1/FVC ratio were documented in the 2 groups. Knight-Madden et al\(^{8}\) also noted similar findings in their study. The limitation of using FEV1/FVC ratio in isolation to determine the severity of obstructive lung disorder has been reported. As both FEV1 and FVC may decline with the progression of SCD. Fonseca et al\(^{21}\) also noted decreased lung volume parameters in SCA children, they reported that in SCA, abnormal lung function may be present with airway reactivity implicated in its pathogenesis. While restrictive physiology is a normal finding in adults, Koumbourlis et al\(^{22}\) also noted that children with SCA may present

### Table 2 - Statistical analysis of pulmonary function indices 40 subject with SCA and 40 matched controls.

| Parameters | Subjects (n=40) | Control (n=40) | P-value |
|------------|----------------|---------------|---------|
| FEV1 (litres) | Mean±SD | Range | Mean±SD | Range | 0.0007 |
| FVC (litres) | 1.60±0.5173 | 0.7 - 0.70 | 2.01±0.5301 | 1.7 - 3.20 |
| FEV1 (%) | 91.70±11.89 | 44.9 - 101.6 | 94.77±5.453 | 78.8 - 100 |
| FVC | 309.00±82.64 | 160 - 490 | 364.10±87.85 | 210 - 590 | 0.005 |

### Table 3 - Pulmonary function test values according to gender among 40 subject with SCA and 40 matched controls.

| Parameters | Males | Controls | P-value | Females | Controls | P-value |
|------------|-------|---------|---------|---------|---------|---------|
| FEV1 (litres) | 1.65±0.57 | 2.05±0.63 | 0.042* | 1.55±0.47 | 1.96±0.42 | 0.006 |
| FVC (litres) | 1.82±0.67 | 2.15±0.66 | 0.125 | 1.70±0.47 | 2.08±0.42 | 0.01 |
| FEV1 (%) | 91.40±12.10 | 95.49±3.95 | 0.228 | 91.30±11.90 | 94.00±6.65 | 0.381 |

### Table 4 - Forced expiratory volume in one second (FEV\(_1\)) according to age groups for subject with SCA and matched controls.

| Age group (years) | Subjects (n=40) | Control (n=40) | P-value |
|-------------------|----------------|---------------|---------|
|                  | n | Mean (FEV\(_1\)) | SD | Range | n | Mean (FEV\(_1\)) | SD | Range |
| 6-10              | 7 | 1.18 | 0.2189 | 0.90-1.5 | 7 | 1.56 | 0.3474 | 1.07-1.96 | 0.0093 |
| 11-15             | 23 | 1.52 | 0.4143 | 0.70-2.4 | 24 | 1.93 | 0.4537 | 1.18-3.11 | 0.391 |
| 16-20             | 10 | 2.14 | 0.5240 | 1.55-2.7 | 9 | 2.55 | 0.4092 | 2.04-3.2 | 0.077 |

### Table 5 - Forced vital capacity (FVC) according to age groups among 40 subject with SCA and 40 matched controls.

| Age group (years) | Subjects (n=40) | Control (n=40) | P-value |
|-------------------|----------------|---------------|---------|
|                  | n | Mean (FVC) | SD | Range | n | Mean (FVC) | SD | Range |
| 6-10              | 7 | 1.40 | 0.5567 | 0.95-2.56 | 2 | 1.62 | 0.3749 | 1.09-2.15 | 0.624 |
| 11-15             | 23 | 1.65 | 0.3904 | 1.14-2.53 | 4 | 2.07 | 0.4790 | 1.18-3.39 | 0.065 |
| 16-20             | 10 | 2.40 | 0.5025 | 1.75-3.50 | 9 | 2.65 | 0.4055 | 2.07-3.32 | 0.253 |
with obstructive phenomenon, yet over 30% of them with reduced lung function present with a restrictive pathology. Some authors have attributed the lower values of lung function indices in HbSS patients to the fact that they have a shorter thorax relative to body size as well as a narrower lateral chest diameter compared with controls of same ethnicity.23 These differences in thoracic and lung volumes results in a reduction in the ratio of total lung capacity (TLC) to vital capacity in the HbSS patients.

The finding of comparable lung function between the HbSS males and females is similar to those of a previous study.18 Previous study concluded that gender may not be a very important determinant of pulmonary function in the HbSS patients. Similar to findings in the present study, previous study,18,19 have also reported marginally, but not significantly higher values of lung function tests in healthy males compared with healthy females with HbAA genotype. In the contrary, Oko-Ose et al14 found significantly higher mean values of respiratory function tests in females compared with the males. The higher values of weight and body surface areas in females explained the gender variations. Some workers19 reported a plateau effect in lung function of normal males and females at a certain age in life, which is believed to be variable.19 This plateau effect was noted at 23 years for males and 19 years for females. When PEFR in controls in the present study compared with previously reported19 values in healthy subjects, comparable values were observed in both genders, but significantly higher than values predicted by Onadeko et al20 at certain heights. Some study18,19 concluded that SCD is associated with the development of a restrictive lung defect. Also highlighted that there was an increasing evidence that this is not a universal finding and that at least during childhood and adolescence when growth is optimal, the majority of the patients have a normal or obstructive pattern of lung function.20 In the present study, the PEFR in the control females were comparable with the values in the previous study19 and maintained consistently, but marginally higher levels except between 135-147.9 cm and 161-173.9 cm where values were significantly higher than those predicted by Onadeko et al.20 One can therefore surmise that PEFR in the Caucasian population approximated those in the present study in both gender. At higher heights in the males, Caucasian values 24,25 seemed to overtake those of the present study. A reduction in lung volume of 1-2% in the sitting position compared with the standing position has been reported by previous studies.19-20 This effect is noted to be higher in obese persons.

The observation of comparable PEFR values in the present study compared with Caucasian values did not come entirely as a surprise despite previous reports of higher values of lung function parameters in most Caucasian studies compared with studies in Africans.23,24 Reasons deduced for this previous higher values of lung function tests in Caucasians compared with Africans include differences in environmental conditions such as nutrition, infections, as well as genetic differences in chest size, shape, and possibly lung volumes.20,24 Although previous studies25 reported the adverse effects of low socio-economic class on lung function tests, in the present study the socio-economic spread of the SS patients and matched controls were comparable. Any differences in the lung function were therefore observed, unlikely to result from differences in social class between the 2 groups.

**Study limitations.** This study would be stronger and more accurate if we used a bigger sample size; however, this is limited by the number of children with SCA registered in our teaching hospital. A community or a multi-center study would be worthwhile.

In conclusion, the lung function indices were significantly lower in children and adolescents with SCA compared with matched controls with hemoglobin genotype HbAA. These findings will help to establish baseline values of lung function among children with SCA in this region, and will form a platform for further studies. It is further hoped that the use of current methods of assessing lung function such as helium dilution and body plethysmography will help determine the actual lung pathology in the subjects under study.

### Table 6 - Peak expiratory flow rate (PEFR) according to age groups among 40 subject with SCA and 40 matched controls.

| Age group (years) | Subjects (n=40) | Control (n=40) | P-value |
|-------------------|----------------|---------------|---------|
|                   | n | Means±SD | Range  | n | Means±SD | Range  |
| 6-10              | 7 | 243.60±53.012 | 175 - 315 | 7 | 270.42±48.370 | 210 - 320 | 0.342 |
| 11-15             | 23 | 297.54±72.423 | 160 - 470 | 24 | 352.47±61.327 | 250 - 500 | 0.007 |
| 16-20             | 10 | 390.45±67.154 | 310 - 490 | 9 | 467.97±69.529 | 370 - 590 | 0.024 |
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