Lung function abnormalities in patients with sickle cell disease in a Nigerian tertiary health centre

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**ABSTRACT**

Introduction: Pulmonary complications with the subsequent lung function abnormalities occur commonly among sickle cell disease (SCD) patients even while at their steady states. This study, therefore, aimed to determine the prevalence and pattern of lung function abnormalities and its associated factors among SCD patients.

Methods: This was a hospital-based cross-sectional study in a Nigerian tertiary hospital involving 113 SCD participants and age- and gender-matched non-SCD controls. Spirometry, transthoracic echocardiography, oxygen saturation, complete blood count, serum urea and creatinine were done for the participants.

Results: The forced vital capacity, forced expiratory volume in 1 second and the peak expiratory flow rate of the SCD participants were significantly lower than that of the control group with p-values of 0.004, 0.000 and 0.000 respectively. Of the SCD participants, 40.7% recorded abnormal lung function with the restrictive pattern occurring most commonly with a prevalence of 28.3%. There was a statistically significant relationship between age and lung function of the SCD participants (p = 0.044).

Conclusion: Lung function abnormalities occur frequently among people with SCD with the restrictive pattern being the most common abnormality and these abnormalities occur more frequently as these patients age.

1. Introduction

Sickle cell disease (SCD) represents a group of inherited autosomal recessive conditions of the blood with significant public health interest worldwide, especially in sub-Saharan Africa [1–3]. Globally, at year 2010, SCD is estimated to occur in about 300,000 births annually with an estimated 80% of the births occurring in sub-Saharan Africa where Nigeria has the greatest burden of the disease with over 90,000 births per year [4]. It is most common in malaria-endemic regions of the world with an estimated 10–40% of the population being carriers of the hemoglobin S gene [1].

Although sickle cell disease affects several organs of the body, the lung is one of the main organs involved and pulmonary complications of SCD are very common among SCD patients. They are a common source of morbidity and mortality, being responsible for over 20% of mortality among these patients [5,6]. The repeated occurrence of vaso-occlusive events in patients with SCD is the major pathophysiological factor leading to ischemia, inflammation, vascular proliferation, endothelial dysfunction, and oxidative stress [7]. These mechanisms result in circulatory abnormalities in many organ systems including the pulmonary circulation which is a major site for hypoxic and ischemic injury [8]. In addition, the lung is a major site for fat embolism and venous thromboembolism [9,10]. These factors, in addition to the increased risk of pneumonia, result in the various pulmonary complications seen in these patients [8,9]. These complications, which could be acute or chronic, include venous thromboembolism, acute chest syndrome, asthma, pulmonary hypertension, and sickle cell chronic lung disease [9]. These pulmonary complications are responsible for a variety of pulmonary function abnormalities characterized by restrictive lung disease, obstructive lung disease, hypoxemia and abnormal diffusion capacity and its attendant increased mortality [11,12].

Lung function abnormalities have been observed to occur frequently in a significant proportion of patients with SCD even while at their steady states [13]. The prevalence of these pulmonary dysfunction varies [14–16]. Abnormalities in pulmonary function have been suggested to be the first sign in people with sickle cell chronic lung disease (SCCLD) and early detection of these abnormalities through screening may be...
associated with a reduction in the mortality associated with this condition [17]. Spirometry is a relatively simple and inexpensive pulmonary function test that is readily available and it has a fairly high sensitivity in detecting lung function abnormalities. This study, therefore, aimed to evaluate the prevalence and type of lung function abnormalities using spirometry and its associated factors in SCD patients seen at the Hematology clinic of a Nigerian tertiary hospital compared with healthy non-SCD controls.

2. Materials and methods

This was a hospital-based cross-sectional study done over 12 months at the Hematology clinic of a tertiary hospital in Ogbomoso, Nigeria. The study involved all consenting SCD patients aged 6 years and above who met the inclusion criteria and who were in their steady state. Steady state was defined as the absence of infection, acute episodes of vaso-occlusive crises, stroke, acute coronary syndrome, priapism, and acute splenic sequestration at least 1 month prior to recruitment and having no blood transfusions in the previous 4 months before inclusion in the study [18]. Excluded were those acutely ill, those with unacceptable spirometry, those with chronic respiratory or cardiac disease, those who were current cigarette smokers at that time or who had a prior significant cigarette smoking history (smoked at least 400 sticks of cigarette in their lifetime or at least one stick of cigarette daily for 1 year), pregnant women, those with musculoskeletal disorders capable of influencing the lung function and those who or their guardians refused to give consent. The study involved 113 SCD participants, including 62 children and 51 adults. The result of hemoglobin electrophoresis was confirmed in their medical records. A similar number of age- and gender-matched non-SCD controls were picked from amongst the medical students of the hospital, apparently healthy children seen at the children out-patient department and staff of the hospital. Ethical approval was given by the Research Ethics Committee of the Hospital.

Socio-demographic data and history items of the SCD participants were collected after obtaining consent using a structured interviewer-administered questionnaire. The weight and height were measured using a GIMA® ASTRA weighing scale with an incorporated height meter after ensuring minimal dressing (extra clothing such as caps, headgears, wristwatches and foot wears were removed) and this was used to determine their body mass index (BMI). Patients with respiratory symptoms were excluded using a modified Medical Research Council (MRC) questionnaire for respiratory symptoms [19]. The MRC questionnaire is a 17-item questionnaire on respiratory symptoms (such as breathlessness, cough, phlegm and wheeze), including detailed questions on smoking history and a checklist on previous illnesses. A general physical, cardiovascular and respiratory system examination was done to also exclude those with musculoskeletal, cardiovascular and respiratory abnormalities that can affect lung function. Oxygen saturation was measured with a finger probe pulse oximeter (Onyx II 9550° by Nonin) using the index finger of the participant’s right hand. Hypoxemia was defined as oxygen saturation (SPO$_2$) of <90% [20,21]. Blood samples were obtained from the SCD participants and sent to the laboratory for full blood count, urea and creatinine. Transthoracic echocardiography was done by a consultant cardiologist for the SCD participants to determine the maximum tricuspid regurgitant jet velocity (TRVmax) using a Siemens Sonoline Omnia echocardiography machine in conformity with the American echocardiography society guidelines [22]. The average of three different TRVmax measurements was recorded as the TRV value and values ≥2.5 m/s were classified as elevated TRV [23].

Spirometry was done and interpreted for all the participants (study and control groups) in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [24] using a standardized spirometer (MIR Intermedical Spirolab) manufactured by Intermedical (UK) Limited. Each subject was asked to perform the maneuver three times and the best of three spiograms which met the acceptability criteria was selected for measurement of the forced vital capacity (FVC), forced expiratory volume in 1 second (FEV$_1$), peak expiratory flow rate (PEFR) and FEV1/FVC% (ratio of FEV1 to FVC expressed as a percentage) with each parameter being expressed as both absolute and percentage predicted values. Acceptable blows were free of artifacts or coughs, had sharp take-offs and had exhalation duration of >6 seconds (3 seconds in children) or a plateau in the volume-time curve. Normal FEV1, FVC and PEFR were defined as values ≥80% of predicted values (customized in the spirometer) as given by Knudson et al [25]. Normal FEV1/FVC% was defined as a value ≥80%. The result of the procedure was classified based on ATS guidelines as normal if FEV1, FVC and FEV1/FVC% were normal; obstructive if FEV1/FVC% was <70%, restrictive if FEV1/FVC % was normal with a low FEV1 and FVC or mixed pattern if FEV1, FVC and FEV1/FVC% were low. Patients with abnormal spirometry were referred to the pulmonology clinic for further evaluation and management.
The data obtained were analyzed using the Statistical Package for Social Sciences (SPSS) version 23.0 (IBM Corp., Armonk, NY, USA) and were presented in frequency tables and charts. Continuous variables such as age, FVC and FEV₁ were expressed as means ± standard deviation. The relationship between categorical variables was assessed for statistical significance using Pearson chi-square. Student t-test was used to assess means of continuous data for statistical significance. A p-value of ≤ 0.05 was considered significant.

3. Results

3.1. Basic characteristics and lung function of the participants

One hundred and thirteen (113) participants took part in the study comprising 62 (54.9%) children and 64 (56.6%) males with a mean age of 18.1 ± 9.85 years. Only 13 (11.5%) were on hydroxyurea. The most frequent complication as obtained in the participants’ medical record was chronic osteomyelitis with a frequency of 22.1% while the least was hemiparesis with a frequency of 12.4%. Of the SCD participants; 40.7% recorded abnormal lung function with the breakdown revealing that 28.3% had the restrictive pattern, 11.5% had obstructive pattern while 9.9% had the mixed pattern. (Table 1)

3.2. Mean BMI and lung function of both the study and control groups

The mean BMI of the SCD participants was 17.59 ± 3.56 kg/m² and this was significantly lower than that of the control group which was 20.98 ± 5.16 kg/m² with a p-value of 0.000. The mean FEV₁, FVC and the PEFR of the SCD participants were 2.07 ± 0.718 L, 2.55 ± 1.096 L and 4.59 ± 2.184 L/min respectively and it was significantly lower than that of the control group with values of 2.87 ± 2.796 L, 3.05 ± 0.959 L and 5.73 ± 2.549 L/min respectively with p-values of 0.004, 0.000 and 0.000 respectively. The % predicted values for FVC, FEV₁ and PEF were also significantly lower among the SCD participants as compared to the control group. (Figure 1)

| Variables                        | Frequency n (%) | n = 113 |
|----------------------------------|----------------|---------|
| Age (in years)                   |                |         |
| 6–17                             | 62 (54.9)      |         |
| ≥ 18                             | 51 (45.1)      |         |
| Sex                              |                |         |
| Male                             | 64 (56.6)      |         |
| Female                           | 49 (43.4)      |         |
| Daily use of folic acid          | 108 (95.6)     |         |
| Use of malaria prophylaxis       | 87 (77.0)      |         |
| Use of hydroxyurea               | 13 (11.5)      |         |
| History of complications         |                |         |
| Acute chest syndrome             | 17 (15.0)      |         |
| Chronic osteomyelitis            | 25 (22.1)      |         |
| Avascular necrosis               | 20 (17.7)      |         |
| Hemiparesis                      | 14 (12.4)      |         |
| Lung function                    |                |         |
| Normal                           | 67 (59.3)      |         |
| Restrictive                      | 32 (28.3)      |         |
| Obstructive                      | 13 (11.5)      |         |
| Mixed                            | 1 (0.9)        |         |

Table 1. Basic characteristics and lung function of the SCD participants.

| Factors                                      | Frequency (n) | Percentage (%) |
|----------------------------------------------|---------------|----------------|
| PCV Mean ± SD (%)                            | 24.15 ± 4.56  |                |
| WBC Mean ± SD X 10⁹ (cells/L)               | 13.52 ± 6.22  |                |
| Platelet Mean ± SD X 10¹³ (cells/L)         | 327.13 ± 151.97 |              |
| Urea Mean ± SD (mmol/L)                     | 3.51 ± 1.40   |                |
| Creatinine Mean ± SD (µmol/L)               | 91.36 ± 35.10 |                |
| TRVmax (m/sec)                               | 106           | 93.8           |
| <2.5                                         | 7             | 6.2            |
| ≥2.5                                         | 14            | 12.4           |
| Hypoxemia                                    | 20            | 17.7           |
| Frequency of crisis                          | 93            | 82.3           |
| ≤ once/year                                  |               |                |
| > once/year                                  |               |                |
| History of blood transfusion                 | 80            | 70.8           |

Table 2. Laboratory and clinical parameters of the study participants.

Figure 1. Lung function of the SCD and non-SCD groups.
3.3. Laboratory and selected clinical parameters and history of complications

The mean packed cell volume (PCV), serum urea and creatinine were 24.15 ± 4.56%, 3.51 ± 1.40 mmol/L and 91.36 ± 35.10 μmol/L respectively. The mean TRVmax was 1.71 ± 0.78 m/sec. Of the SCD patients, 82.3% of them had a frequency of vaso-occlusive crisis which was >once/year and 70.8% of them had a history of blood transfusion. (Table 2)

3.4. Relationship between study participants’ basic characteristics, complications and lung function

The number of adults with abnormal lung function was significantly higher than that of the children (p = 0.044). There was no significant relationship between lung function and gender, BMI and history of complications. (Table 3)

3.5. Relationship between the participants’ clinical and laboratory parameters and lung function

There was no significant association between participants’ lung function and frequency of vaso-occlusive crisis, hypoxemia, PCV and TRVmax. (Table 4)

4. Discussion

The study shows that the lung function and BMI of patients with SCD were significantly lower than their non-SCD controls and that abnormal lung function is common among these patients occurring with a prevalence of 40.7% with the most common abnormality being the restrictive pattern which was seen in 28.3% of the study participants.

Generally, people with SCD have been observed to have a lower BMI than their unaffected peers [15,26]. For instance, in a study by Olatunji-Bello et al it was observed that the mean BMI was significantly lower in the sickle cell patients as compared with the non-SCD health controls [26]. This finding is similar to that of our study where we observed a mean BMI of 17.59 ± 3.56 kg/m² among people with SCD and this was significantly lower than the control group who had a mean BMI of 20.98 ± 5.16 kg/m². The relatively lower BMI has been suggested to be due to the adverse effect of chronic anemia on development among patients with SCD [26].

Our study also revealed that lung function parameters (FEV1, FVC% and PEFR) were significantly lower in SCD participants compared to the non-SCD controls and this aligns with findings from earlier studies [13,14,27]. Anthropometric characteristics, particularly weight and BMI are some of the determinants of lung function. We believe that the smaller lung volumes observed in this study are due to the significantly lower BMI among SCD patients as earlier highlighted in this study. Furthermore, it has also been earlier suggested that as a result of frequent infarctions in the vertebral, sternum and ribs with subsequent impairment of optimal growth and development,
patients with SCD have relatively smaller chest wall as compared to their non-SCD counterparts and this may further contribute to a reduction in lung volumes [28].

In this study, it was observed that 40.7% of our study participants had abnormal lung functions with the restrictive pattern being the most common abnormality. Our observed value of 40.7% is lower than the 71% and 70.4% reported by Ozoh et al in Lagos, Nigeria and Dei-Adomakoh et al in Ghana respectively [14,15]. However, it is greater than the 28.5% observed by Adekile et al in Kuwait [16]. As earlier stated, the prevalence of abnormal lung function varies among people with SCD. The reason for this difference may be due to the different methodologies employed in the various studies. For instance, the mean age of the participants in the study by Adekile et al was 10.5 ± 3.2 years; ours was 18.1 ± 9.85 years while that of Dei-Adomakoh et al was 33.7 ± 11.11 years. Generally, lung function abnormality tends to occur more frequently with increasing age [29,30]. The reported prevalence in these studies tends to increase with an increasing mean age. Hence, this may be responsible for the different prevalence reported by these studies. It is not unexpected that the restrictive pattern was the most common abnormality observed. The restrictive pattern is defined by a reduction in lung volumes (FEV1 and FVC) and as earlier discussed; patients with SCD have reduced lung volumes compared to their non-SCD counterparts. Only 11.5% of our SCD patients had obstructive defects and this is comparable to the 16% reported by Dei-Adomakoh et al [15]. The etiology of the obstructive defect in patients with SCD is more complicated and rather unclear but it is believed to be due to hypoxia, inflammation and oxidative stress on the airways [31].

In our study, we also observed that there was a significant association between age and lung function. It was observed that 67.7% of children with SCD had normal lung function as compared to 49% of adults who had normal lung function. This finding is not unconnected to the fact that lung function has been observed to decline with age even in people with SCD [29,30]. This may be due to the recurrent infarctions in the lungs, ribs, sternum and vertebra as a result of repeated vaso-occlusive crisis with resultant reduction in lung elasticity, chest wall expansion and ultimately restrictive defect. These events have been shown to worsen as the individual gets older [12].

We found no significant association between lung function abnormality and participants’ selected clinical histories such as frequency of crisis, transfusion history, routine use of hydroxyurea and history of complications such as acute chest syndrome, chronic osteomyelitis, avascular necrosis and hemiparesis. There was also no significant association between lung function and TRVmax, oxygen saturation and laboratory parameters including PCV, WBC, platelet count, urea and creatinine.

In conclusion, our study has shown that lung function abnormalities occur quite frequently among people with SCD with the restrictive pattern being the most common abnormality and that the abnormal lung function occurs more frequently as these patients age. We also observe that the abnormal lung function has no significant relationship with markers of disease activity such as frequency of crisis, history of acute chest syndrome, chronic osteomyelitis and packed cell volume.

We recommend early-onset periodic screening with spirometry to aid early detection and further management.

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