

**ASSESSMENT OF PULMONARY**  
**FUNCTIONS IN PATIENTS WITH**  
**SICKLE CELL ANEMIA IN STEADY STATE**  
**AT KENYATTA NATIONAL HOSPITAL**

**A DISSERTATION TO BE SUBMITTED IN PART FULFILMENT**  
**FOR THE DEGREE OF MASTER OF MEDICINE IN INTERNAL**  
**MEDICINE, UNIVERSITY OF NAIROBI.**

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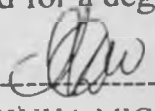
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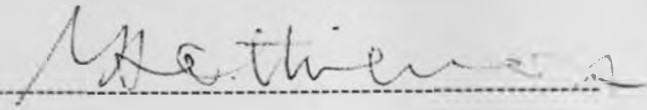
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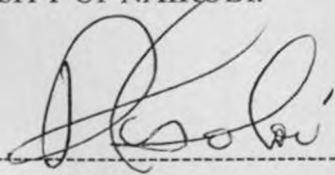
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## DEDICATION

To my father Elijah Mukuha, my wife Josphine and my two sons Roy and Lewis for their invaluable support and encouragement.

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## ABSTRACT

**Introduction** Sickle cell anemia is one of the most common genetic disorders with more than 200 million carriers of sickle cell traits worldwide. With increasing survival into adulthood there has been an increase in chronic organ failure and the lung is among the major organs involved contributing to significant mortality and morbidity

**Main objective** To determine the prevalence and severity of pulmonary dysfunction in patients with sickle cell anemia in steady state at K.N.H.

**Study design** A cross sectional comparative study.

**Case definition** Confirmed SCA patients on HB electrophoresis who were 12 years and above and the controls were life long non smokers matched for age and sex.

**Study population** A total of 160 cases comprising 80 SCA patients and an equal number of controls were recruited.

**Method** History was taken and physical examination done. Spirometry was done and their TLC, RV, FEV1, FVC, FEV1/FVC ratio and resting pulse oximetry were taken

**Results** Eighty (80) sickle cell anemia patients in stable state and eighty (80) healthy controls were studied. The mean age of the SCA patients was 17.35 +/- 3.49 with a range of 12-42 years. The majority comprising 58.8% were in the age group of 12 up to 19 years with only 6.2 % being above 30 years of age. The male to female ratio was 1:1.

SCA patients had significantly reduced TLC, RV, FEV1%, FVC% with an increased FEV1 to FVC ratio in keeping with a restrictive defect. The restrictive defect also showed significant negative relationship with number of crises and number of transfusions.

**Conclusion** SCA patients have predominantly a restrictive pattern of pulmonary dysfunction.



## LITERATURE REVIEW

Sickle cell anemia is a genetic disorder that was first reported in literature in 1910 by Herick, a Chicago cardiologist (1). He described a West Indian student with peculiar and elongated sickle shaped cells, a cardiac murmur and severe anaemia.

Sickle cell anemia encompasses a group of hemoglobinopathies characterized by a single amino acid substitution in the  $\beta$  globin chain. The most frequently occurring form is sickle cell anaemia [HB SS] followed by hemoglobin sickle C [HB SC] disease and sickle B thalassaemia.

The sickle cell syndromes are caused by a single gene mutation in the  $\beta$  globin chain that changes the 6<sup>th</sup> amino acid from glutamic acid to valine.

The mode of inheritance is either autosomal recessive or autosomal dominant with variable penetrance and expressivity. The disease usually manifests in the homozygous state but in some situations may be observed in the heterozygous state if HbS is greater than or equal to 40% (2).

Sickle cell anemia [SCA] is one of the most common genetic disorders (3).

There are more than 200 million carriers of sickle cell trait worldwide, and 200,000 to 300,000 people are born annually with major hemoglobinopathies(4). Approximately 0.14% of African American children are homozygous for the sickle cell gene. In the US 6-10% of African American newborns have sickle cell trait making SCA the most prevalent inherited disorder in African Americans (1, 5).

Hemoglobin S gene is found mainly among the Negroid community and non Negroes in Turkey, southern Italy, northern Greece, eastern province of Saudi Arabia and India. (6). In Africa the distribution runs in the equatorial belt from ocean to ocean including Madagascar (6-8). In Kenya the gene has

a clustering around the lake Victoria basin and the Coast Province affecting mainly the Luo, Luhya, Nyika, Pokomo, and Taveta tribes with an average frequency ranging from 0-30% (7,9,10)

SCA is a major cause of morbidity and mortality in Africa, affecting the lives of 1 % of all children born in tropical Africa causing their early death while contributing to 80,000 infant deaths per year (7). In a study of 38 SCA patients in Nairobi, Mwangemi found that the majority (63.1%) were below 20 years with the oldest being 33 years and 1 ½ year mortality rate of 5.26% making him conclude that SCA patients suffer early deaths (8). Jacob found that the chances of survival to adulthood were 14% in Uganda and 35% in Kenya in 1957 among the SCA patients (36).

Between 1987 and 1990 in a study of 3605 patients with SCA, Aluoch and Aluoch found that 77% of the patients were below age fifteen with the oldest being a 50 year old female (11). They found that 80% of the patients were of Luo or Luhya ethnic group (Luo 58.4%, Luhya 23.9%). They also found a discrepancy between sickle cell trait rate (SCTr) and the percentage distribution of SCA patient per province. The Kambes of the Mijikenda group in the coast province with the highest SCTr (35%) constituted only 8.5% but the Luos with a SCTr of 28% made 58% of the total SCA patient population in Kenya (11).

With improved supportive care the median age of survival has risen to 42 years for men and 48 years for women in north America (12). As survival into adulthood has become more common in patients with sickle cell anemia there has been an increase in chronic complications including chronic organ failure (12,13). HBSS polymerizes reversibly under low oxygen tension, low pH (acidosis), increased levels of 2,3 diphosphoglycerate or hypertonicity to form a gelatinous network of fibrous polymers that stiffen the erythrocyte

membrane, increase viscosity and cause dehydration due to potassium leakage and calcium influx. During their passage in circulation red blood cells containing HbS go through a series of cycles of sickling and unsickling and finally due to changes in membrane permeability the cells become irreversibly sickled. These changes lead to the characteristic sickle shape of the red blood cells (2). Sickled cells lose their deformability and are therefore unable to traverse small capillaries and venules (2). They possess altered "sticky" membranes especially reticulocytes that are abnormally adherent to the endothelium of small venules (2). Vaso-occlusive phenomena and hemolysis are the hallmarks of HbSS.

The lung is among the major organs involved in sickle cell anemia (14-16). Pulmonary complications account for a large proportion of deaths among patients with sickle cell anaemia. According to the cooperative study of sickle cell anaemia (CSSCD), more than 20% of adults had fatal pulmonary complications of sickle cell anaemia (12). The cooperative study on sickle cell disease is the largest single study on sickle cell disease to date. This was a prospective multicentred study that collected clinical data on 4082 sickle cell disease patients in various centres in the United States of America from 1978 up to 1988. Patients were followed up for an average of 5.2 +/- 2 years. Age specific prevalence rates and incidence rates of the various complications of SCD were analysed including their pulmonary functions.

Acute and chronic pulmonary complications occur frequently in patients with sickle cell anemia and represent the most common cause of death in adulthood (12). Although the pathogenesis of pulmonary disease in SCA has not been clearly defined, recurrent microvascular obstruction resulting in the development of pulmonary hypertension and parenchymal fibrosis is the most likely primary underlying pathophysiologic mechanism.

Airway hyper-reactivity is a common pulmonary function test abnormality among young subjects with SCA. The reported incidence of obstructive lung defects in children with SCA is 35% to 37% (17, 18). Prospective controlled study demonstrated airway reactivity to cold air in 60% patients with SCA compared with none in the control population, suggesting an association between SCA and airway reactivity (17). The pathogenesis of increased airway reactivity and its relation with ACS and SCCLD however is unknown.

Nocturnal oxyhemoglobin desaturation has been reported in SCA subjects with a prevalence of up to 40% in children and adolescents (19, 20). Proposed mechanisms are obstructive sleep apnoea, intrinsic lung disease and an abnormality in oxyhemoglobin affinity (20). Several investigators have documented obstructive sleep apnoea in SCA with or without nocturnal oxyhemoglobin desaturation.

Patients with SCA are known to be hypercoagulable. The sickle haemoglobin (HBS) is poorly soluble once deoxygenated. The polymerisation of HBS is essential to vasoocclusion. The polymer assumes the form of an elongated rope like fibre resorting in distortion into the classic crescent or sickle shape and a marked decrease in red cell deformability (3, 21). Pulmonary thromboembolism may contribute to both ACS and SCCLD (3). Although thromboembolism has been noted in 8%-25% of autopsy studies in patients with SCA, the exact incidence and prevalence is unknown (13, 15).

Clinical lung involvement manifests in two major forms. Acutely primary pulmonary diseases in sickle cell anemia include infections / pneumonia, infarction due to in-situ thrombosis, embolic phenomenon due to fat emboli or bone marrow infarction and acute chest syndrome (14-16).

Distinguishing among these illnesses in the patient who presents with an acute respiratory process is difficult. It is clear however that recurrent vascular and parenchymal insult constitute the greatest risk factors for the development of sickle cell chronic lung disease.

ACS is defined as the appearance of a new pulmonary infiltrate on chest radiograph accompanied by fever and a combination of respiratory symptoms that include cough, tachypnoea and chest pain (21-24). It is the second most common cause of hospitalization in patients with SCA and responsible for up to 25% of deaths (13, 25, 26). ACS has been reported to occur in 15% to 43% of patients with SCA. Moreover, recurrent episodes occur in 80% of those who have had a prior episode (25,27). The incidence is age related with rates of 24.5 events per 100 patient years in young children with HbSS and decreasing to 8.8 events per 100 patient years in older subjects (25,27). ACS rates vary directly with steady state leukocyte counts and hemoglobin concentration, and inversely with age and hemoglobin F levels (25).

The cooperative study of sickle cell anemia which prospectively followed up 3751 patients reported data on 1722 ACS episodes in 939 patients (25). Patients with ACS presented with fever (80%), cough (74%), chest pain (57%), Dyspnoea (28%), productive cough (24%), wheezing (11%), and haemoptysis (2%) accompanied by hypoxia, leukocytosis, and infiltrates on chest radiographs that often progressed to multi lobar pulmonary disease indistinguishable from acute respiratory distress syndrome.

The exact incidence, prevalence, natural history and methods of diagnosis of sickle cell chronic lung disease (SCCLD) have not been established due to the lack of detailed epidemiological studies. It is suggested that SCCLD has a prevalence of approximately 4% in patients with SCA (16, 28). SCCLD is

presumably related to recurring episodes of infarction and infection and is characterized by a decrease in radiolucency of the lungs, moderate to severe impairment of pulmonary function, and in its most severe form by evidence of pulmonary hypertension (16, 29,30).

Post mortem studies of patients with SCA often show evidence of pulmonary vascular bed obliteration, smooth muscle hypertrophy, and parenchymal fibrosis (19).

Significant radiographic interstitial lung disease has been seen in patients with SCA (13, 14). In a prospective study, 41% patients with SCA who had at least one prior episode of ACS were found to have significant multifocal interstitial lung abnormalities on CT scans of the chest (28). A correlation was found between the severity and extent of interstitial abnormalities on CT scans and the number of prior episodes of ACS.

Sickle cell chronic lung disease may begin to develop as early as the 2<sup>nd</sup> decade of life (26, 31, and 32). Pulmonary dysfunction rapidly progresses with death occurring within seven years of diagnosis (26, 31, and 32)

Significant risk factors for SCCLD include recurrent episodes of acute chest syndrome, painful crises and aseptic bone necrosis (14-16).

Patients characteristically progress through four clinical stages based upon physiologic and radiographic data and symptoms (32)

Stage 1 is associated with a recurrent chest pain and cough, mild reductions in FVC and TLC (70-79%of predicted), normal oxygen saturation and near normal (slightly increased interstitial markings) chest radiographs.

Stage 2 is associated with greater pain than stage 1, moderate reductions in FVC and TLC (50-69% of predicted), normal oxygen saturation and diffuse interstitial fibrosis (all lobes by chest X-ray).

Stage 3 is associated with severe crushing chest pain, hypoxaemia during unstable periods, severe reductions in FVC and TLC (less than 49% of predicted), and pulmonary fibrosis on chest X-ray.

Stage 4 is characterized by prolonged chest pain, fixed dyspnoea, hypoxaemia at rest, severe pulmonary fibrosis on chest X-ray and elevated pulmonary artery pressure.

Many different parameters of pulmonary function are altered in patient with sickle cell lung disease. As examples, total lung capacity (TLC) and vital capacity (VC) may be reduced (33, 34).

Even when corrected for the anaemia, the diffusion capacity of carbon monoxide (DLCO) is abnormally low, particularly in patients with a history of the acute chest syndrome (33, 34).

Arterial oxygen saturation ( $\text{SaO}_2$ ) is reduced with mean baseline values below 90%.

The alveolar-arterial difference is widened both at rest and with exercise which most likely results from ventilation and perfusion abnormalities (26).

Mild to moderate airflow obstruction may be present, particularly among patients with recurrent episodes of ACS.

Pulmonary function abnormalities in SCA are frequent and are characterized by airway obstruction, restrictive lung disease, abnormal diffusion capacity and hypoxemia, (17, 33, 35, 36). However, a restrictive airway abnormality is typically seen in patients with SCCLD (17, 33, 35, and 36).

Unfortunately there is currently no therapy known to reverse the severe restrictive lung disease observed among patients with sickle cell disease. It is however possible to reduce the number of sickling crises by aggressively utilizing the available treatment options and thereby reduce or delay the

onset of the pulmonary dysfunction. Increased awareness of the existence of the condition may also give impetus to drive the aggressive management and possibly lead to development and trial of new treatment modalities.

In sickle cell traits, although organ dysfunction is rare pulmonary infarction as well as sudden death during intense military training has been reported (31). However, no difference in exercise tolerance and pulmonary function either at sea level or at altitude has been observed between patients with sickle cell trait and matched normals (29). In addition no current data supports occupational, military, or athletic restriction in patient with sickle cell traits (3)



## STUDY JUSTIFICATION

Sickle cell anemia is one of the commonest genetic disorders in the world. According to the cooperative study of sickle cell disease (CSSCD), more than 20% of adults had fatal pulmonary complications of sickle cell anaemia both acute and chronic.

Although pulmonary manifestations of SCA are common, they remain under-diagnosed by physicians.

No studies have been done in Africa to assess the prevalence and severity of pulmonary dysfunction in patients with SCA.

This information gap needed to be filled.

This would further increase the knowledge base and form a firm basis for routine assessment, increased recognition and early detection of onset of the condition.

## **HYPOTHESIS**

There is no difference in pulmonary function between patients with sickle cell anemia and normal age and sex matched controls.

## MAIN OBJECTIVE

The main objective was to determine the prevalence and severity of pulmonary dysfunction in patients with sickle cell anemia in steady state.

## SPECIFIC OBJECTIVES

1. To determine the forced expiratory volume in one second ( $FEV_1\%$ ), the forced vital capacity (FVC%), the total lung capacity (TLC), the residual volume (RV), the ratio of forced expiratory volume in one second to the forced vital capacity ( $FEV_1/FVC\%$ ) in patients with SCA in steady state at K.N.H. and compare with normal age and sex matched controls.
2. To determine the resting oxygen saturation in patients with SCA at K.N.H. and compare with normal age and sex matched controls.
3. To determine the relationship between the forced expiratory volume in one second ( $FEV_1\%$ ), the forced vital capacity (FVC%), the total lung capacity (TLC), the residual volume (RV) and the ratio of forced expiratory volume in one second to the forced vital capacity ( $FEV_1/FVC\%$ ) with age, number of crises in the previous one year and number of transfusions in the previous one year in patients with SCA at K.N.H.

## METHODOLOGY

### STUDY DESIGN

This was a cross sectional comparative study

### SAMPLE SIZE ESTIMATION

The sample size was calculated using the formula on appendix 3. The minimum number needed was calculated at one hundred and fifty subjects.

One hundred and sixty were recruited (160). Eighty (80) SCA patients were recruited and an equal number of age and sex matched controls.

### STUDY AREA

This was a hospital-based study and was conducted at the hematology out patient clinic of **Kenyatta National Hospital (K.N.H)**.

**K.N.H** is a tertiary referral hospital for KENYA located in NAIROBI the business and political center of the country. Though most of the patients seen at K.N.H. live in Nairobi, a good proportion are referred from the outlying districts and provinces. The hematology out patient clinic provides a forum for regular follow-up of all patients with sickle cell anemia.

### STUDY POPULATION

These were patients with sickle cell anemia aged 12 years and above in steady state and on follow-up at K.N.H. and an equal number of age and sex matched controls.

## **STEADY STATE - DEFINITION**

Steady state in SCA patient was defined as a state of no identifiable active disease process clinically and /or crises or any major complications and where these exist, to be such that they did not have any direct effect on the study procedures and / or on the study variables. No laboratory parameters were used in the definition in this study.

## **PATIENT SELECTION**

### **INCLUSION CRITERIA**

Patients were included in the study if they had a diagnosis of sickle cell anemia on hemoglobin electrophoresis.

They had to be 12 years old and above.

An informed written consent was required and for minors a fully informed consent was obtained from the parent and/or guardian.

Those that were decisionally impaired were only included if a legally authorized representative provided a fully informed consent.

### **EXCLUSION CRITERIA**

Those unable to understand or follow instructions as relates to spirometry, patients with obvious chest deformities, known asthmatics, known HIV positive patients and smokers – either current or those who had smoked in the past.

The other group of patients excluded were those with relative contraindications to spirometry including haemoptysis of unknown origin, pneumothorax, those with history of unstable angina pectoris or recent myocardial infarction, recent eye surgery and / or recent abdominal or thoracic surgical procedures. Patients with a history of syncope associated

with forced exhalation or patients with any other condition(s) that were deemed to have an effect on the study procedure or on the study variables were also excluded. Those patients who declined consent were also excluded.

### SAMPLING PROCEDURE

The investigator reviewed all files of patients with sickle cell anemia in steady state presenting at the hematology clinic. All the files were selected and issued with numbers. Using table of random numbers, six (6) were then picked for inclusion in the study provided they met the inclusion criteria.

Eligible patients were randomly recruited into the study until the sample size was achieved. Patients from the hematology clinic were interviewed on Monday between 9am and 11am every week.

Controls matched for age and sex were recruited from among patients in surgical, ophthalmological and orthopaedic wards being admitted for elective procedures and their pulmonary functions were assessed before they were taken to theatre to ensure that they were not in pain. The patients were only recruited if their conditions were painless and would have no bearing either on the study procedure or on the results of pulmonary functions such as, patients with lipomas, small hernias, hydrocoeles, cataracts and exostosis among others.

These were life long non smokers and with no respiratory symptoms and/or signs.

People who identified themselves as being members of Luo and Luhya ethnic groups were excluded to reduce the possibility of inclusion of sickle cell trait among the control group.

### STUDY DURATION

The period of patient recruitment and data collection was between April 2006 and September 2006.

### CLINICAL PROCEDURE

Patients recruited were requested to sign the consent form (Appendix 3).

They then underwent a thorough history and physical examination.

Those recruited and consenting to the study from the hematology clinic were then taken to the respiratory laboratory in the afternoon of the same day for spirometry and pulse oximetry.

The history included such demographic data as the name, age, and sex, as per the study proforma. History of any illnesses at that time was taken as well as any history of crises that had occurred in the past one year- specifically the type of crisis, its severity and the number of the crises experienced. History of any blood transfusions in the one year prior to recruitment was also taken. Further history was taken to rule out the presence of any of the relative contraindications to spirometry.

A thorough physical examination was then done and the patient's height was recorded.

Controls matched for age and sex were recruited from among patients in surgical ophthalmological and orthopaedic wards being admitted for elective procedures and their resting oxygen saturation was assessed. Their demographic data was taken and they were then subjected to spirometry on the same day before they could be taken to theatre to ensure that they were not in pain. The patients were only recruited if their conditions were painless and were not expected to have any bearing either on the study procedure or on the results of pulmonary functions such as, patients with lipomas, small

hernias, hydroceles, cataracts and exostosis among others. (Those who identified themselves as being members of the Luo or Luhya communities were excluded)

They were people who were life long non smokers and with no respiratory symptoms and/ or signs. They were required to give informed written consent and were subjected to similar procedures as the test group as outlined above.

## **LABORATORY METHODS**

### **SPIROMETRY**

The patients were instructed by the investigator and/or the respiratory laboratory technician to inhale as much as possible and then exhale rapidly and forcefully for as long as flow could be maintained. The assessment of the total volume of air exhaled from a full lung (total lung capacity [TLC] to an empty lung [residual volume]) was done. The model of spirometer used was master screen V4.34.

The forced vital capacity (FVC) and the forced expiratory volume in one second ( $FEV_1$ ) were to be reproducible to within 0.2 L upon repeat efforts for acceptable spirometry. A valid end point was defined by meeting one of three criteria. (1) Smooth curvilinear rise of the volume time tracing to a plateau of at least one second duration. (2) If the test failed to exhibit an expiratory plateau, a forced expiratory time (FET) of 15 seconds; or (3) when the patient could not continue forced exhalation for valid medical reasons.

This was done in the respiratory function laboratory in ward 7C. Attention was focused on the following parameters; Forced vital capacity(FVC), Forcefully exhaled volume in 1 second ( $FEV_1$ ), and the ratio of the

forcefully exhaled volume in one second and the forced vital capacity (FEV<sub>1</sub>-to-FVC %), the total lung capacity (TLC) and the residual volume (RV). Abnormalities were then classified by the following physiologic patterns.

### **OBSTRUCTIVE DEFECTS**

Obstructive lung defect is defined by a normal or increased TLC, an increased RV, a reduced FEV<sub>1</sub> and a reduction in the FEV<sub>1</sub> as compared to the FVC (and therefore the FEV<sub>1</sub>-to-FVC ratio, also called the FEV<sub>1</sub>%)

Where an obstructive pattern was noted inhaled bronchodilators were to be given to assess reversibility. They were however not given as no obstructive defect was observed.

### **RESTRICTIVE DEFECTS**

Restrictive lung diseases were defined by a reduced TLC, RV, and a reduction in the FVC with a normal or elevated FEV<sub>1</sub>-to-FVC ratio.

Quantification of the impairment by spirometry was based on reductions in the FVC and/or the FEV<sub>1</sub> and were characterized as being mild if the FVC was between 70-79% of predicted.

They were characterized as moderately severe if the FVC was between 50-69% and severe if  $\leq 49\%$  of predicted

**PULSE OXIMETRY** by use of oximeter probes placed on fingers or earlobes to assess oxygen saturation was done in the respiratory laboratory in ward 7C by the investigator and/or the respiratory laboratory technician.

**HEIGHT** was taken with a tape measure with the subject standing against a wall without shoes.



### STUDY VARIABLES

The study variables included the TLC, RV, FEV<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC%

Others included the oxygen saturation, the number of transfusions in the past one year and the number of painful crises.

The physiologic pattern of respiration, age and gender were also included.

### DATA MANAGEMENT AND ANALYSIS

Data was coded and entered into a microcomputer using SPSS/PC+ version 10 programme. Data validation was done before analysis. Analysis involved descriptive statistics such as means, medians and standard deviations for continuous variables and proportions and frequency distributions for categorical variables.

Study population were described in terms of age, gender, hemoglobin level, oxygen saturation level, frequency of crises and their severity, number of transfusions and the physiologic pattern of respiration. Point prevalence was determined as percentages of the study population. For continuous variables that were normally distributed the T-test was used. Where the variables were not normally distributed the Mann Whitney U test was used. For categorical data Chi-square test was used. Associations were measured and considered statistically significant at a P- value of less than 0.05.

## ETHICAL CONSIDERATIONS

The study was only undertaken after approval by the department of internal medicine, University of Nairobi and the Kenyatta National Hospital ethics and research review committee. Cases eligible to participate in the study were included after going through the consent process which included their being told the purpose of the research.

The procedure of the study was explained clearly with full details of the tests to be done.

It was explained that participation was voluntary and that no medical attention would be denied should they decline to participate

The subjects were informed of the medical benefits and also any physical and or psychological harm to their satisfaction prior to being included in the study

Therapeutic interventions were recommended where the need arose, according to accepted standards of practice.

It was asserted that confidentiality would be strictly maintained, and the subjects were assured of full and free access to their results and that all data would be securely stored and only revealed upon a need to know basis.

They were assured that all costs regarding the investigations were being borne by the principal investigator.

Following the full explanation and acceptance by the patient of the above, the subject was requested to sign the consent form (appendix 3).

Minors (less than 21 years) were required to give their own consent and also to have additional consent by the parent/guardian

## RESULTS

Eighty (80) sickle cell anemia patients in stable state and eighty (80) healthy controls were studied.

The sickle cell anemia patients were recruited from among those coming for regular follow-up in the hematology out patient clinic.

The controls were age and sex matched to the SCA patients.

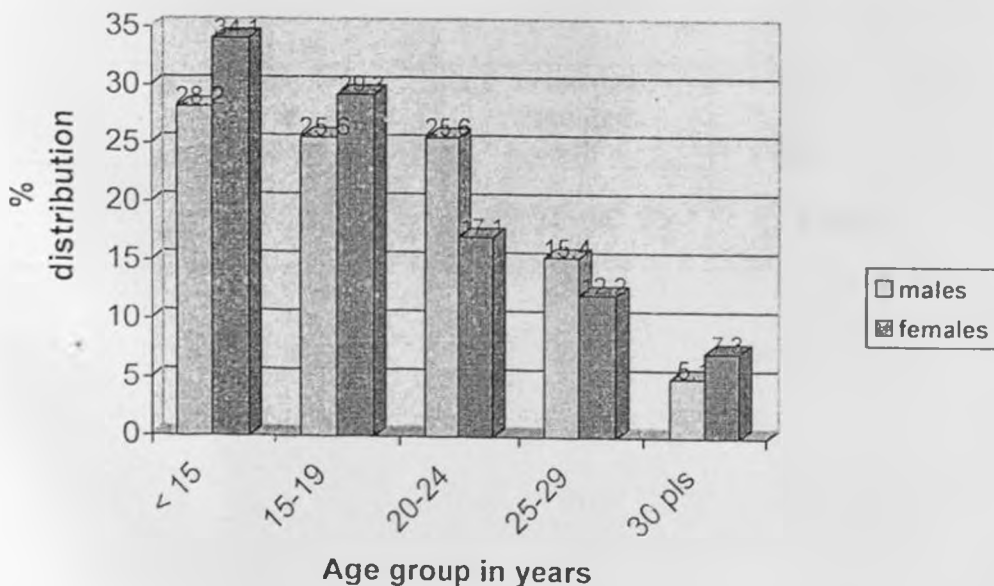
Among the SCA patients 39 were males comprising 48.6% of the population and females were 41 comprising 51.4% of the population.

The mean age of the SCA patients was 17.35 +/- 3.49 with a range of 12-42 years.

The majority making up 58.8% were in the age group between 12 and 19 years with only 6.2 % being above 30 years of age.

The detailed age distribution is as shown in figures 1.

Fig 1 ;Age and sex distribution among the SCA group



## HEIGHT

The mean height of the patients with SCA was 159.6 +/- 9.24cm with a range of 140 to 180cm.

In the control group the mean height was 161cm +/-9.93 with a range of 144cm up to 185cm. This height difference was not statistically significant at a p value of 0.602 (Table 1)

## OXYGEN SATURATION

The mean oxygen saturation among the SCA patients was 91.3% +/-2.49% with a range of 88% up to 96%.

In the control group the mean oxygen saturation was 96.5% +/-0.96% and had a range of between 95% and 98%. (This difference was statistically significant. P at  $\leq 0.001$ ). (Table 3)

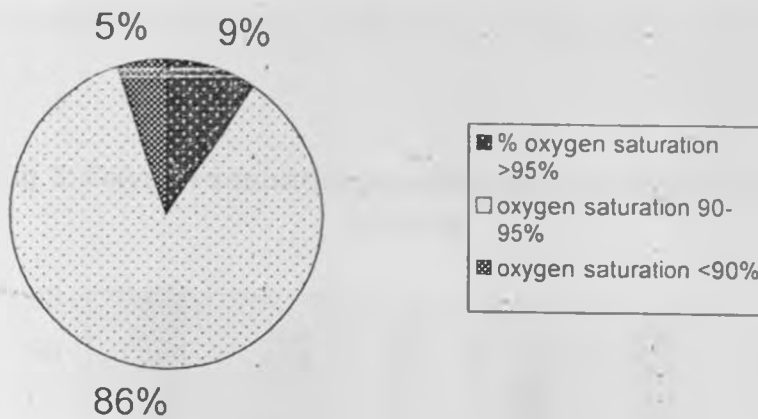
**Table 1; Oxygen saturation between SCA group and the controls**

	% oxygen saturation (SCA)	% oxygen saturation (Control)	P value
Mean	91.33 +/-2.49	96.59 +/-0.96	<b>0.0001</b>

Overall only 7 cases (9.3%) of SCA patients had oxygen saturation above 95%.

The majority of the cases (85.3%) had their oxygen saturation between 90 and 95% while 4 cases of SCA (5.3 %) had their oxygen saturation below 90% with the lowest at 88% (Figure 2).

**Figure 2:Oxygen saturation among the SCA group**

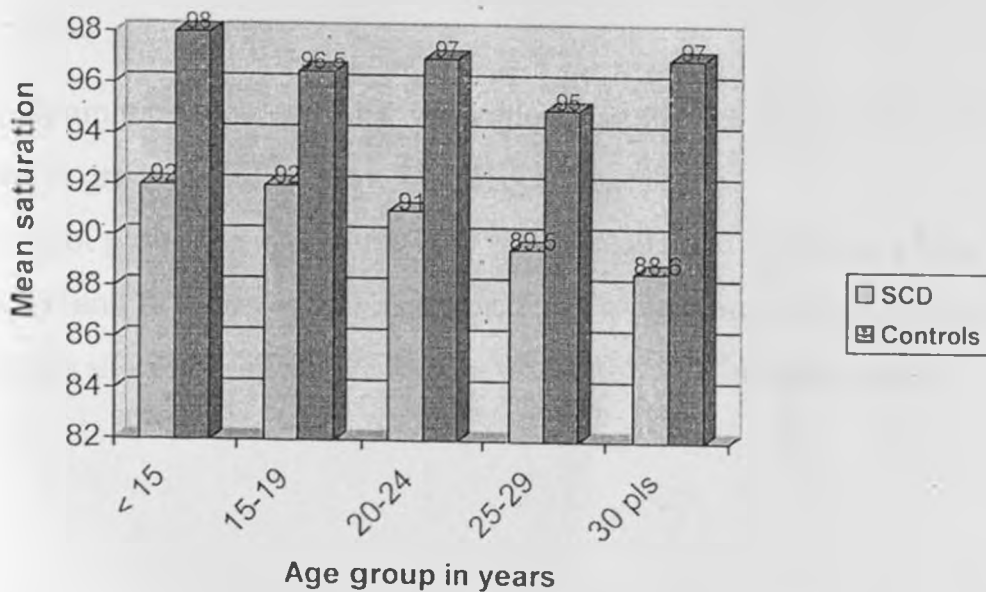


Oxygen saturation among the SCA group attained maximal saturation in the age group between 12 years up to 19 years with the mean saturation being 92% and thereafter was noted to have progressive decline with increasing age.

In the control arm the maximum saturation was noted in those between 12 years and 15 years with the mean saturation at 98%. There was however no significant change with increasing age. (Figure 3)

The difference in saturation between the SCA group and the controls achieved statistical significance.  $P$  at  $\leq 0.01$  (Table 1)

Fig 3: Oxygen saturation between the SCA group and the controls



## Total lung capacity (TLC)

The mean total lung capacity (T L C) among the SCA was 3.39 litres +/- 0.84 litres with a range of 1.56 litres up to 5.62 litres with a median of 3.31. In the control group the mean T L C was 4.75 litres +/-1.03 litres with a range of between 3.05 litres and 6.62 litres and a median of 4.33. This was statistically significant. P at  $\leq 0.001$  (Table 2).

**Table 2; TLC between the SCA group and the controls**

	TLC (SCA)	TLC (Control)	P value
Mean	3.39 +/- 0.84	4.75 +/- 1.03	0.0001

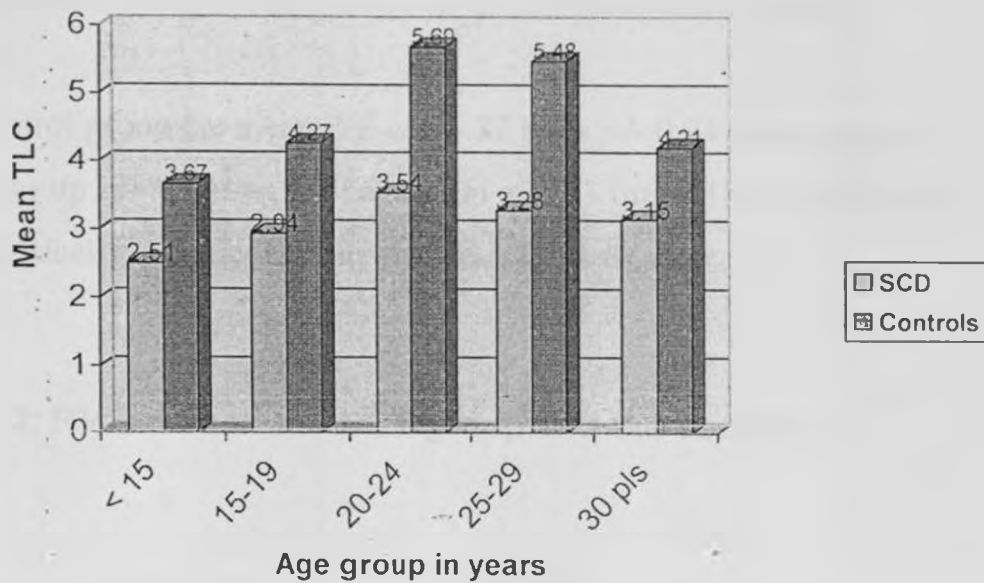
The maximum total lung capacity was achieved in the age group 20-24 years for the SCA group with the mean TLC at 3.54 litres.

In the control group the maximum TLC was also attained in the age group between 20 and 24 years with the median TLC in the group being 5.8 litres.

Both groups showed progressive decline thereafter with increasing age.

(Figure 4)

Fig 4: TLC between the SCA group and the controls





## RESIDUAL VOLUME (R V)

The mean residual volume (RV) among the SCA patients was 0.95 litres +/- 0.23 litres with a range of 0.33 liters up to 1.37 litres and a median 0.94litres.

In the control group the mean RV was 1.27 litres +/- 0.24 and a range of 0.922 litres up to 1.65 litres with a median of 1.21 litres. These differences were statistically significant. P at  $\leq 0.001$ . (Table 3).

**TABLE 3; RV between the SCA group and the controls**

	RV (SCA)	RV (Controls)	P value
Mean	0.956+/-0.23	1.276 +/- 0.24	<b>0.001</b>

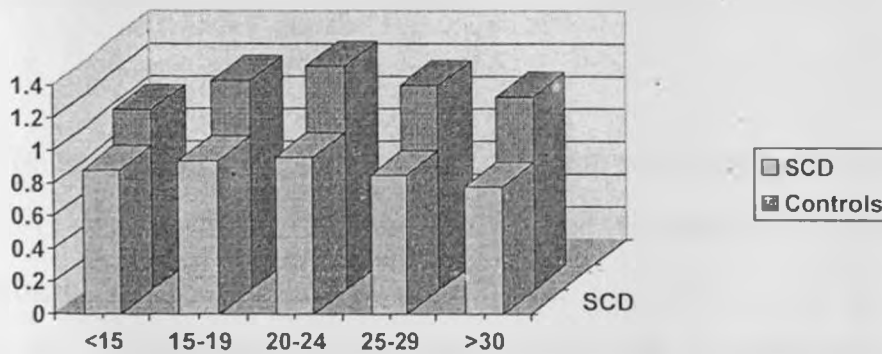
## RESIDUAL VOLUME (RV) Vs AGE

The residual volume (RV) and age distribution followed a similar pattern to the total lung capacity (TLC) with the maximum volume being attained in the age group 20 – 24 years for both the SCA group and the controls with the mean RV for the SCA group being 0.97 litres while the mean RV among the controls was 1.27 litres.

The difference achieved statistical significance ( $P \leq 0.001$ ).

Thereafter there was progressive decline of RV with increasing age in both the SCA group and controls (Figure 5).

**Figure 5; Mean RV between the SCA group and the controls**



Age group in years

### FORCED EXPIRATORY VOLUME IN ONE SECOND (FEV1%)

The mean FEV1% among the SCA patients was 70.1% +/- 10.75% with a range of 34.5% and 89% and a median of 72%.

In the control group the mean FEV1% was 88% +/-4.91% with a range of between 80% and 98% and a median of 87%.

This was statistically significant. P at  $\leq 0.001$  (Table 4).

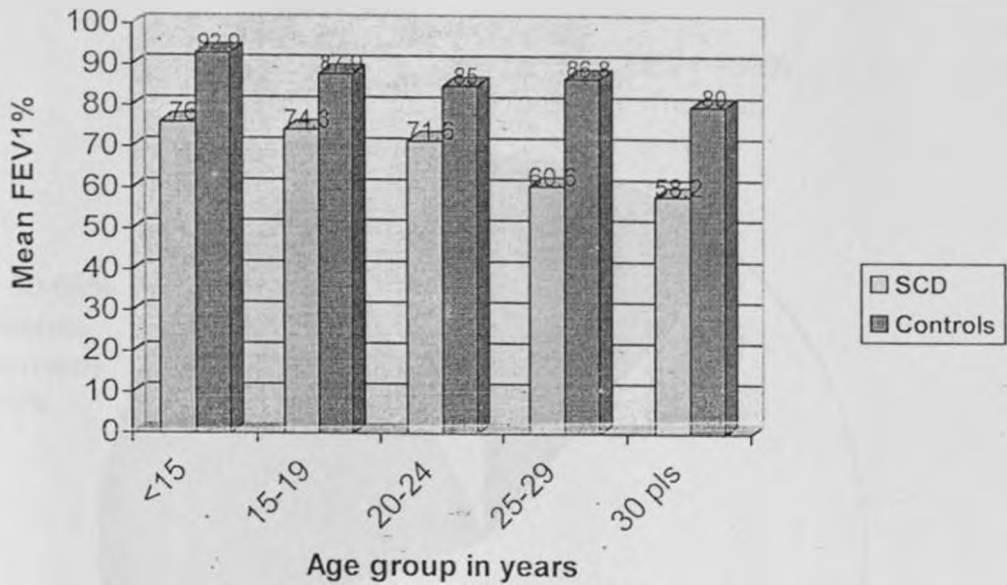
**TABLE 4; FEV1%between SCA group and the controls**

	FEV1% (SCA)	FEV1% (Control)	P value
Mean	70.12 +/-10.8	88.04 +/-4.9	0.001

The maximum FEV1% for the SCA group was achieved in the age group 12-15 years with the mean being 76% and it subsequently showed progressive decline with increasing age.

In the control group the maximum FEV1% was also attained in the age group 12-15 years with the mean being 92.9% and it exhibited a plateau thereafter (Figure 6).

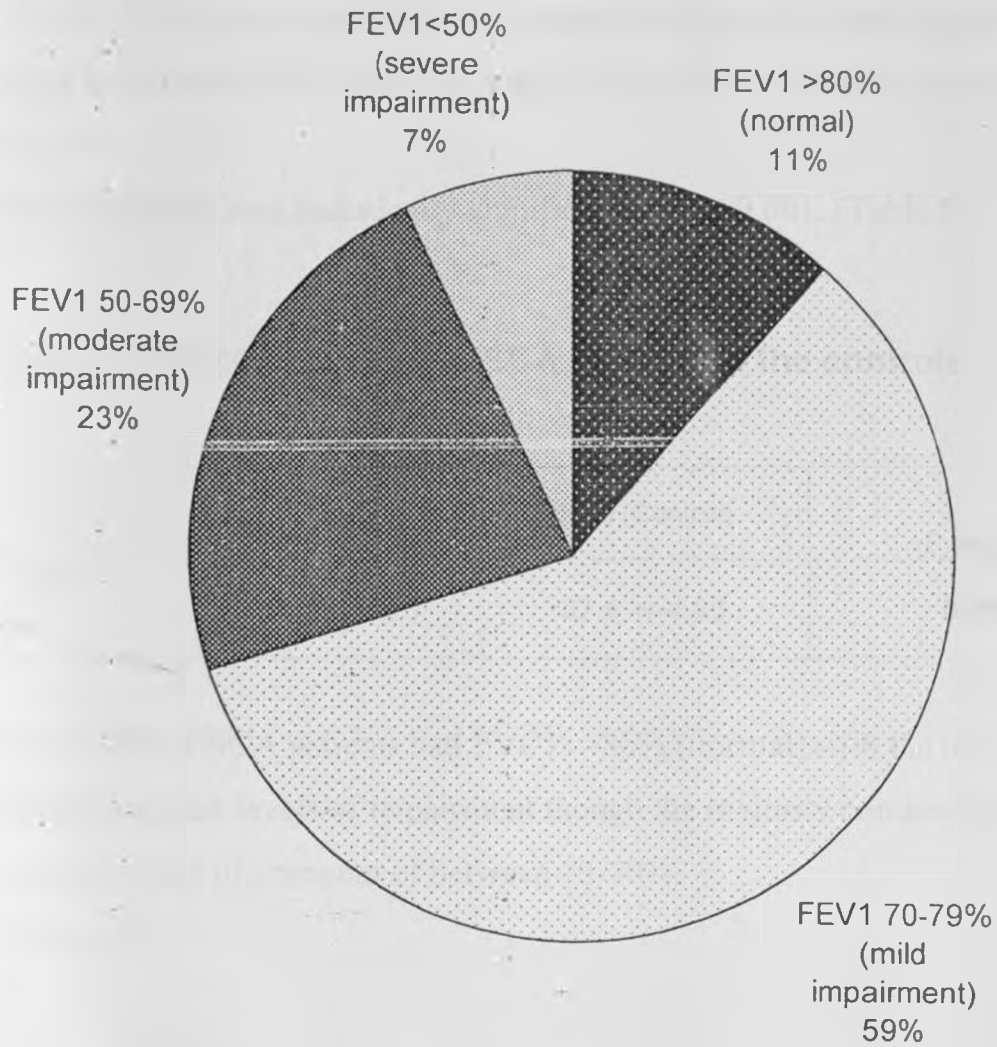
Fig 6: FEV1% between the SCA group and the controls



Among the SCA patients, 11.3% of them had an FEV1%  $\geq$  80% (normal), 58.8% had FEV1% range of between 70 and 79 % ( mild dysfunction). Those with moderate impairment i.e. FEV1% of between 50 and 69% were 22.6%, while 7.3% had an FEV1% of below 50 % ( severe impairment). (Figure 7).

In the control arm all had FEV1% of  $\geq$  80%.

Figure 7: FEV1% distribution among the SCA group



### FORCED VITAL CAPACITY (FVC %)

FVC%, among the SCA patient ranged between 28%-90.8% with a mean of 64% +/-12.1% and a median of 63% whereas among the control group the range was between 79-98% with a mean rate of 87% +/-4.96% and a median of 89 %.

This difference was statistically significant. P at  $\leq 0.001$ . (Table 5)

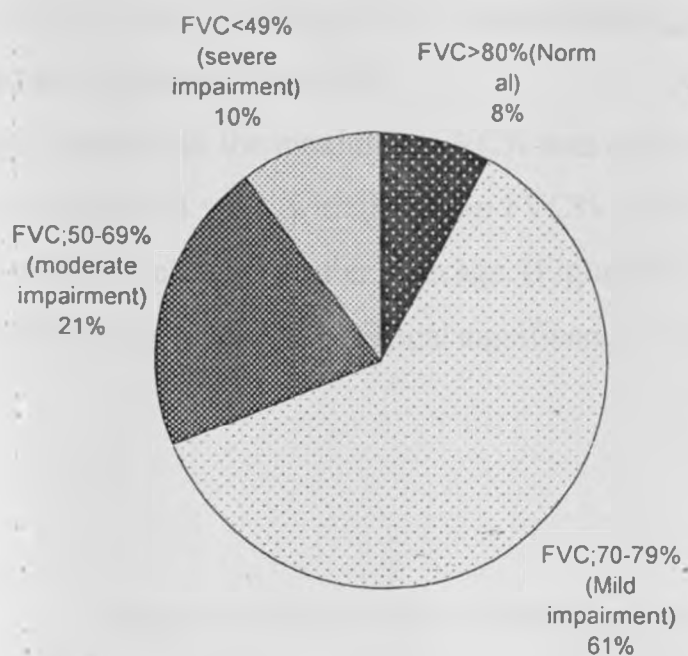
**Table 5: FVC% between the SCA group and the controls**

	FVC% (SCA)	FVC% (Control)	P value
Mean	64.2 +/-12.1	87.4 +/-4.96	<b>0.000</b>

Only 7.8% of SCA patients had FVC% >80% (normal) with the rest showing varied levels of impairment though the majority comprising 61% had only mild impairment of between 70-79%.

= (Figure 8)

Figure 8 ; FVC% distribution among SCA patients



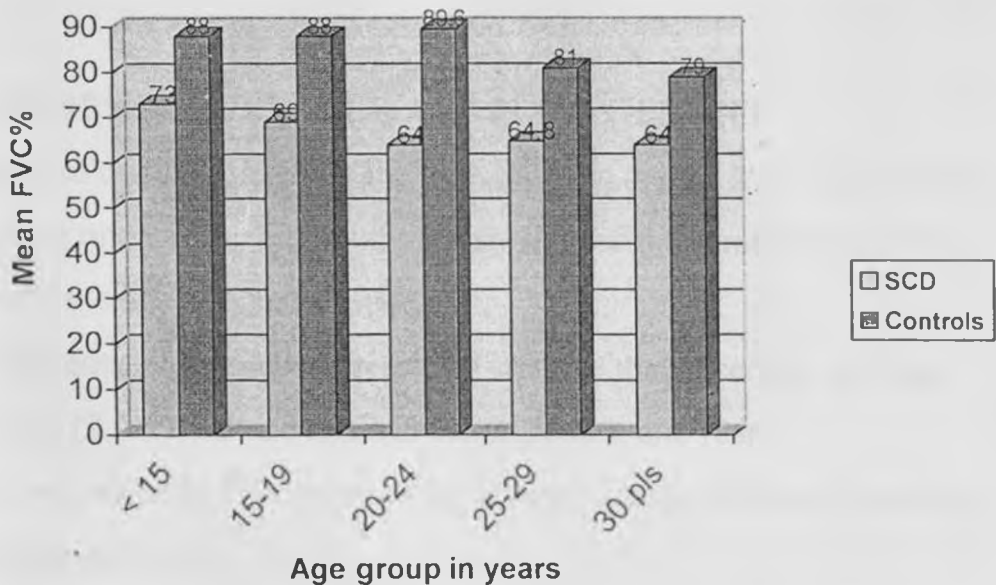
In the control group 97.6 % had their FVC% above 80% (normal). The remaining 2.4% had their FVC% between 70% and 80%.

FVC% exhibited a similar pattern as noted with FEV1% in respect of the SCA group with the peak occurring in the age group with less than 15 years which had a mean FVC% of 73%. This exhibited progressive decline thereafter with age (Figure 10).

In the control arm the maximum FVC% was observed in the age group of 20 years up to 24 years with the mean FVC% of 89.6%. It showed progressive decline thereafter with age. (Figure 9)

The difference achieved statistical significance. P at  $\leq 0.001$ .

Fig 9: FVC% between the SCA group and the controls





### FEV1: FVC %

The FEV1/FVC % among the SCA patients ranged between 89% and 93% with a mean rate of 90.2% +/-16.3% and a median of 91%.

In the control group it ranged between 78% up to 82% with a mean of 80% +/- 5.8% and a median of 80%.

This was statistically significant.  $P \leq 0.001$  (Table 6)

**TABLE 6; FEV1 to FVC% between SCA group and the controls**

	FEV1/FVC % (SCA)	FEV1/FVC% (Control)	P value
Mean	90.2 +/-8.4	80.4 +/- 5.84	<b>0.001</b>

### CRISES OCCURRENCE AND MANAGEMENT

The number of crises suffered by the SCA patients ranged from one crisis in the preceding one year up to a total of nine with the mean rate being 5+/-2 crises with a median of 5 and a mode of 4.

All SCA patients experienced at least one crisis in the preceding one year.

Two patients (2.7%) had one crisis in the preceding one year.

An equal proportion (2.7%) representing another 2 cases suffered 9 crises in the preceding one year.

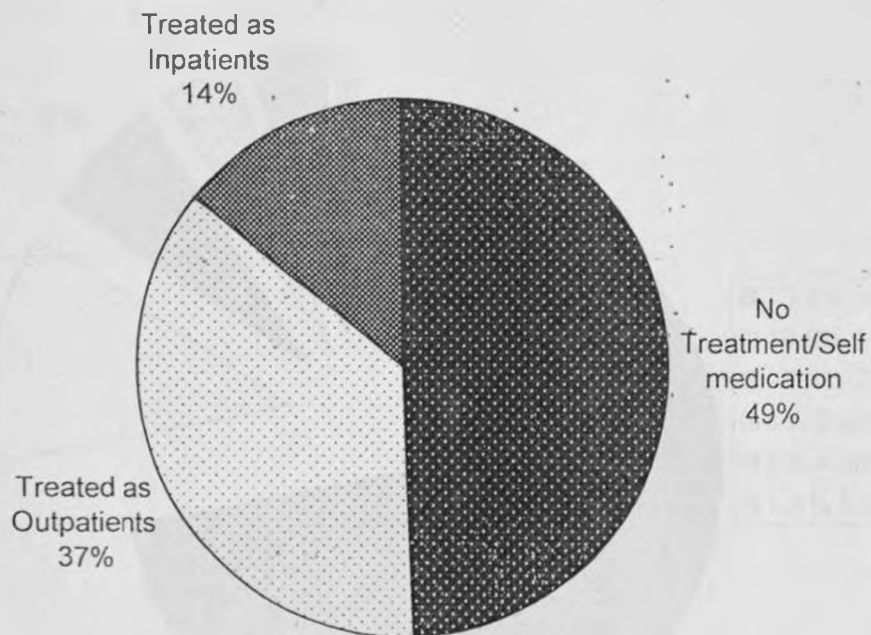
Twenty patients (26.7%) with SCA suffered 4 crises while another twenty (26.7%) suffered 5 crises in the preceding year.

In the event of a crisis 49.7% of the crises suffered were relatively mild and the patients either did not seek medical advice or they self medicated while at home.

In the event of moderate intensity crises, the patients sought medical attention and were treated as out patients and were discharged and this occurred in 36.7 % of the times.

In 14.1% of the times, the crises were severe enough to warrant admission and treatment as in patients. (Figure 10)

**Figure 10; Crises management among SCA patients**



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## TRANSFUSIONS

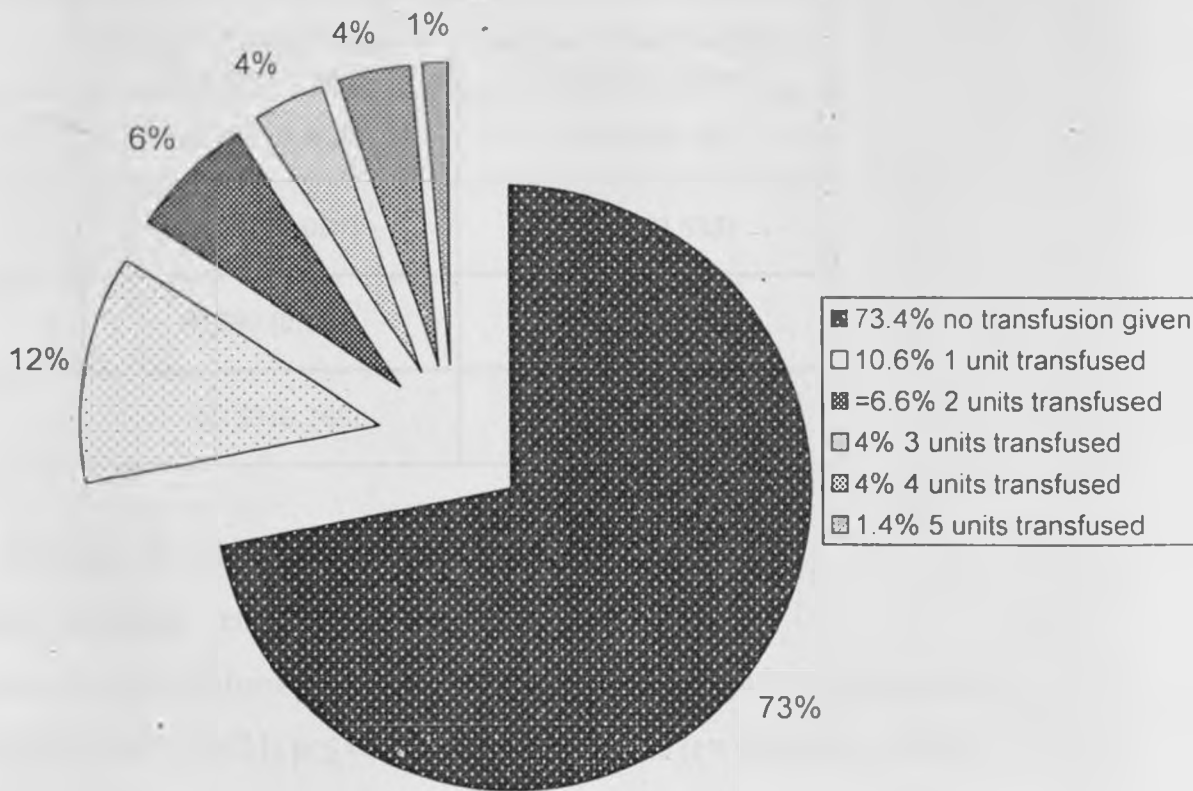
The majority of SCA patients (58) representing 73.4% of the population did not receive any blood transfusion in the preceding one year.

Ten (12.5 %) had been transfused one unit of blood in the preceding one year while five (6.6%) had been transfused 2 units of blood.

Three (4%) received 3 units with an equal number receiving 4 units of blood.

One patient (1.4%) received 5 units of blood. (Figure 11)

**Figure 11: Transfusions among SCA patients**



### Crises correlations

The number of crises was noted to be related to reduction of various parameters that are known measures of lung functions.

TLC was noted to have a significant negative relationship with the number of painful crises ( $r = -0.289$ ;  $p \leq 0.05$ ).

This was also noted in relation to RV ( $r = -0.389$ ;  $p \leq 0.05$ ), and also to FEV1% ( $r = -0.299$ ;  $p \leq 0.05$ )

FVC though reduced and also showing a negative relationship with number of crises did not achieve statistical significance. (Table 7)

**Table 7: Nonparametric Correlations for SCA group**

	number of painful crises in the past 1 year	number of transfusions in the past 1 year
TLC	-0.289 (0.012)	-0.164 (0.16)
RV	-0.389 (0.001)	-0.063 (0.593)
FEV1%	-0.299 (0.009)	-0.421 (0.0001)
FVC%	-0.130 (0.266)	-0.349 (0.002)

#### **KEY**

**( ) in bracket- P value**

**Without bracket – correlation coefficient r**

The number of transfusions also showed significant negative relationship with FEV1% ( $r = -0.421$ ;  $p \leq 0.05$ ) and with FVC% ( $r = -0.349$ ;  $p \leq 0.05$ ).

The TLC ( $r = -0.164$ ) and RV ( $r = -0.063$ ) also showed a negative relationship with number of transfusions and was reduced but it did not achieve statistical significance.

The numbers transfused were however small (26.6%).

**Table 8; SUMMARY TABLE OF LUNG FUNCTION PARAMETERS IN BOTH THE SCA GROUP AND THE CONTROLS**

	SCA group	Control group	P value
Height	159.62 +/- 9.249	161.17 +/- 9.937	0.602
% Oxygen saturation	91.33 +/-2.49	96.59 +/-0.96	0.0001
TLC	91.33 +/-2.49	96.59 +/-0.96	0.0001
RV	0.956+/-0.23	1.276 +/- 0.24	0.001
FEV1%	70.12 +/-10.8	88.04 +/-4.9	0.001
FVC%	64.2 +/-12.1	87.4 +/-4.96	0.0001
FEV1/FVC%	90.2 +/-8.4	80.4 +/- 5.84	0.001

### SUMMARY OF FINDINGS

SCA patients had predominantly a restrictive pattern of pulmonary dysfunction as attested to by the significantly reduced TLC, RV, FEV1% and FVC% with an increased FEV1 to FVC ratio.

Among SCA patients aged between 12 and 15 years a restrictive defect was already evident in more than 70 % of them and by the age of 25 years all had demonstrable and significant restrictive pulmonary dysfunction.

The number of crises and transfusions was noted to have significant negative relationship with the decline in pulmonary function.

None of the SCA patients had an obstructive pattern of respiratory dysfunction.

## DISCUSSION

Sickle cell chronic lung disease (SCCLD) is a prime contributor to both mortality and morbidity in young adult patients with SCA especially those with sickle cell anemia (HBSS) (12). Both perfusion and diffusion defects have been demonstrated with generalized pulmonary fibrosis and disabling restrictive lung failure (21).

The greater majority of those studied comprising 58.8% were in the age group of 12 up to 19 years with only 6.2 % being above 30 years of age. This is related to the high and relatively early mortality that occurs in patients with SCA with few surviving to adulthood and sickle cell chronic lung disease is one of the principle contributors to the early mortality (12). These figures compare well with figures from local studies. Mwangemi in 1977 found that most of the patients were below 15 years of age (8).

Aluoch and Aluoch in a survey of sickle cell anemia in Kenya (1987-1990) found that 77% of the cases were below 15 years (11). This study did not include those below 12 years and therefore cannot give the overall current age distribution among the SCA patients. It was however still observed that 80 % of the population was below 25 years and overall 21.3% were in the age range of 20-24 years which is a significant number going beyond the teenage years. This may be explained partially by improved care and therefore increased survival into adulthood. This is below the median survival age in the united kingdom of 42 years for men and 48 years for women (31).

Height has significant association in terms of absolute measures of lung functions. However between the two group studied there was no significant difference in height and therefore it was not expected to have any influence on the results or their interpretation.

Oxygen saturation was significantly lower among the sickle cell anemia patients in the various age groups as compared to the controls. Also noted was the progressive decline with increasing age. This was noted to be related to the progressive decline in TLC, RV, FEV1% and FVC% which also had progressive decline with age. This was consistent with what Gladwin and co workers demonstrated in a series of 16 adults between 20 and 40 years of age with SCA and no history of pulmonary disease in the physiologic studies at the national institute of health where the mean oxygen saturation was 91% $\pm$  3% (16). This was replicated by Miller JG (33) who did an assessment of lung volumes and gas transfer in sickle cell anemia and found the mean oxygen saturation being 90%  $\pm$  2%.

Among the SCA patients the mean peak oxygen saturation was 92% and this was noted in both the age groups of <15 years and the group between 15-19 years. In the subsequent years it exhibited progressive decline.

Age is a known independent risk factor for reduction in lung functions including oxygen saturation but this is only expected from ages above 30 years (40). Among the SCA patients there was already significant reduction in oxygen saturation by the age of 12 to 15 years with the mean saturation at that age being 92% and it exhibited progressive decline thereafter with increasing age. It was not possible in this study to determine how early the decline in oxygen saturation may have started as there was already significant reduction by 12 years of age which was also the cutoff age in this study. Previous studies have suggested that sickle cell chronic lung disease may begin to develop as early as the second decade of life (26,31,32).

In the control group oxygen saturation was best at ages 12-15 years with the median saturation being 98% and remained in the normal range throughout

thereafter though no significant follow-up occurred after 30 years as the numbers in this age bracket were very few (6.2%)

The reduction in oxygen saturation among the SCA patients is attributable to the recurrent episodes of thrombosis in the pulmonary micro vasculature with the associated repeated infections and infarctions seen in ACS.

Histologically there is alveolar wall necrosis, interstitial organization and fibrosis with intimal thickening of muscular arteries, arterioles and venules.

These are all associated with ventilation- perfusion mismatch (Weil JV and co-workers in their study on pathogenesis of lung disease in SCA) (21).

In addition, with repeated transfusions hemosiderosis in the pulmonary tissues occurs and therefore progressive fibrosis with the associated ventilation perfusion mismatch which would affect oxygenation. It was however not possible in this study to determine how many units of blood the SCA patients had received in their lifetime and therefore whether the critical number of 50 units associated with hemosiderosis had been reached as the transfusion history was only enquired to for the one year preceding the study. Other iron studies which may have ruled in or out hemosiderosis were not carried due to logistic reasons and the history of transfusions was only enquired into as a marker of disease severity.

Over time there is progressive loss of lung elasticity and / or recoil, increasing oxygen blood barrier and with the associated splinting that occurs with repeated infarctions in the ribs, hypoxaemia would be expected to occur.

TLC and age in years had a significant positive linear relationship ( $r= 0.656$ ;  $p \leq 0.001$ ). TLC showed progressive increase with age with the maximum achieved at between age 20-24 years for both the SCA patients and the controls tapering thereafter and showing progressive decline subsequently.



This is the expected pattern though in a study in Australia on healthy adolescents and adult subjects, maximum TLC was attained around the age of 17 -20 years with progressive decline thereafter (37). This difference was not explained by this study but since this trend was noted in relation to the other parameters that are a measure of pulmonary function such as RV, FEV1, and FVC there may be a difference in the maturation patterns of the two populations. This needs further survey.

Other studies done among healthy adults of European descent however showed that the peak TLC and FEV1 was attained between the ages of 19 and 23 years (40) with a plateau thereafter up to 30 years of age and showing progressive decline thereafter. This was largely in keeping with the findings in this study. However the SCA patients exhibited significantly lower levels for all age groups assessed compared to the control group with a statistically significant difference. ( $P \leq 0.05$ ).

RV was also noted to have a significant linear positive relationship with age ( $r=0.633$ ;  $p \leq 0.05$ ).RV followed the same pattern with TLC with a peak for both SCA and control groups at 20-24 years with progressive decline thereafter. However the difference between the controls and the SCA groups in respect to the various age groups and their RV was statistically significant. ( $P \leq 0.05$ ).

The residual volume and TLC were significantly reduced in the SCA group. This is expected in view of the repeated infections and infarctions that occur in sickle cell anemia with possible contribution of pulmonary hemosiderosis culminating in progressive lung fibrosis with reduced lung compliance and therefore restriction (21). This is worsened by reduced compliance of the rib cage as a consequence of rib splinting that occurs with repeated infarctions in the ribs.

In terms of absolute measures of lung volumes, FEV1 followed the same pattern as TLC and RV with maximum volumes seen in the age group of 20-24 years largely because absolute lung volumes are dependent on growth in height and width with maximum rib cage volume occurring in this age group.

Using the reference figures adopted for use at KNH (37) as there are no standardized local figures, overall among the SCA patients, only 11.3 % of them had an FEV1% above 80% which is the accepted normal. The rest (88.7%) had impaired lung function though the majority had only mild impairment. All the 11.3 % who had normal FEV1% were less than 24 years of age with the majority lying between 12 and 15 years. By the age 25 years none of the SCA patients had an FEV1% >80% (normal). This is explained by the various factors mentioned above that are seen in SCA.

In the control arm all had FEV1% of  $\geq 80\%$ .

FVC exhibited a similar pattern with the peak again at between age 20-24 years and declining thereafter. It however had significant difference between the SCA group and the controls with the SCA patients exhibiting significantly lower levels. The difference was statistically significant ( $P \leq 0.05$ ).

FVC % followed the pattern of FEV1% with the maximum attained in the age group 12-15 years among the SCA group. This was therefore the age group with best lung function among the sampled SCA patients though this was still significantly reduced as compared to the controls. Among the controls best lung function on the basis of FVC%, FEV1%, TLC and RV was observed in the age group of 20-24 years.

Only 7.8% of SCA patients had FVC% more than 80% (normal). The remainder (92.2%) had impaired lung function.

This is explained by similar reasons as advanced for the reduced FEV1%, TLC and RV as they all followed the same pattern. This therefore serves to underscore the significant pulmonary dysfunction seen in SCA patients with 92.2 % showing some form of impairment among all the sicklers above 12 years sampled. At 25 years all SCA patients had significant restrictive lung dysfunction (FVC% < 80%, reduced FEV1% <80%, TLC and RV and an increased FEV1/FVC %)

This pattern was described by Femi-pearce in a study of pulmonary functions in sickle cell anemia in the United Kingdom (35).

Santori and co workers (17) demonstrated that 37% of SCA patients had obstructive lung disease. This was not demonstrated in this study where no patient with SCA was noted to have an obstructive defect. Their study was however carried out in children and the subjects included even those with acute chest syndrome which may have influenced the results. Small airway obstruction is however also better excluded through the maximum mid expiratory flow rates (PEF<sub>25</sub> - PEF<sub>75</sub>) which were not done in this study. The number of crises were noted to be related to the reduction of various parameters that are a measure of lung functions. This is because the number of crises is a reflection of the disease severity and therefore the increased chances of micro-embolism and infarction within the pulmonary vasculature. TLC was noted to have a significant negative relationship with the number of painful crises ( $r = -0.289$ ). This achieved statistical Significance ( $p \leq 0.05$ ) This was also noted in relation to RV ( $r = -0.389$ ;  $p \leq 0.05$ ), and also to FEV1% ( $r = -0.299$ ;  $p \leq 0.05$ ) (significant)

However FVC though reduced and also showing a negative relationship with number of crises did not achieve statistical significance. (P at 0.266)

This was consistent with what Aquino and co workers (29) found in their 1994 study of chronic pulmonary disorders in sickle cell anemia where a correlation was found between the severity and extent of interstitial abnormalities on CT scans and the number of prior episodes of painful crises including acute chest syndrome (29).

This was also shown by Weil JV and co workers in their study on pathogenesis of lung disease in SCA patients (21). They noted that the greater the number of sickling crisis or acute chest syndrome, the greater the sludging of blood in the pulmonary interstitium with increased infarction and infection leading to progressive interstitial fibrosis. Sickling in distant sites was also associated with minor thrombo-embolic phenomena and repeated showers of microemboli are associated with repeated micro infarcts which lead to diffuse fibrosis over time (21).

With progressive fibrosis there is reduced lung compliance / recoil and increased oxygen blood barrier and therefore the reduced TLC, RV, FEV1, FVC and oxygen saturation.

The number of transfusions showed significant negative relationship with FEV1% ( $r = -0.421$ ;  $p \leq 0.05$ ) and with FVC ( $r = -0.349$ ;  $p \leq 0.05$ ).

The TLC and RV were reduced in relation to transfusion but did not achieve statistical significance.

Though a correlation with number of transfusion was noted, the number of subjects transfused over the preceding one year was small (26.6%) and the majority of those transfused received only one unit of blood. Therefore though hemosiderosis is one of the known mechanisms contributing to pulmonary fibrosis in SCA patients (21), the numbers in this case and the volume of blood transfused may not support such a conclusion and further iron studies would be needed to support or reject that conclusion.

## CONCLUSION

- 1- Chronic pulmonary complications of SCA are common.
- 2- SCA patients have significantly reduced RV, TLC, FEV1% and FVC% when compared with normal age and sex matched controls and despite this reduction they had significantly increased FEV1:FVC% which is in keeping with a restrictive pattern of pulmonary dysfunction.
- 3- Among SCA patients aged between 12 and 15 years a restrictive defect was already evident in more than 70 % of them while by the age of 25 years all had demonstrable and significant restrictive pulmonary dysfunction.
- 4- SCA patients had significant hypoxemia as measured by pulse oximetry with 90.7% having their oxygen saturation below 95% while among the control group all of them had their oxygen saturation above 95%.
- 5- There is a correlation of pulmonary dysfunction with disease severity as exemplified by the significant negative correlation between the number of crises and the number of transfusions and the various parameters that are an indicator of pulmonary dysfunction.

## STUDY LIMITATIONS

Problems with recall as relates to the number of transfusions and crises in the preceding one year had a theoretical possibility of creating some bias in result interpretation.

The number of units of blood transfused in the lifetime of a sickler is important in relation to hemosiderosis which is a known cause of restrictive lung defect and therefore the issue of recall was relevant. However transfusion history in this study was only enquired into for the preceding one year as it was only used as a marker of disease severity.

The results of the study may not reflect the state of sickle cell anemia in patient living at lower altitudes as this study was carried out at high altitude. Hemoglobin electrophoresis was not done among the controls and there was therefore the theoretical possibility of including sickle cell traits. However, no difference in exercise tolerance and pulmonary function either at sea level or at altitude has been observed between patients with sickle cell trait and matched normals (29).

Small airway obstruction is better excluded through the maximum mid expiratory flow rates ( $PEF_{25} - PEF_{75}$ ) which were not done in this study.

## RECOMMENDATIONS

1. More expansive studies that include pediatric patients are needed to ascertain the actual age of onset of pulmonary dysfunction.
2. The frequency and severity of pulmonary complications in patients with SCA warrants that the patients get pulmonary assessment regularly as part of their overall health care package.
3. Due to the early onset of pulmonary dysfunction and its correlation with number of crises more aggressive measures aimed at reducing the number of crises and their risk-benefit profile should be evaluated. This would be expected to have a significant impact in reducing or delaying the onset of pulmonary dysfunction.
4. Further studies are required to evaluate the impact of the restrictive lung disease in SCA patients in terms of morbidity, mortality and quality of life.

## REFERENCES

1. Herick J.B. Peculiar elongated RBCs in a case of severe anaemia. Arch. Int. Med 1910; 6: 517-521.
2. Braunwald E, Fauci A, Kasper D, Hausa S, Longo DL, Jameson JL. Harrison's principles of internal medicine 15<sup>th</sup> edition, International edition. MacGraw - Hill Medical publishing division .2002. Page 669-670.
3. Embury S H, Hebbel RP, Mohandas N, et al. Sickle cell anaemia; Basic principles and clinical practice. New York Raven press, 1997. Page 154-162.
4. The NHLBI working group. Respiratory diseases disproportionately affecting minorities. Chest 1995; 108:510-554.
5. Farber MD, Koshy M, Kinney TR. Cooperative study of sickle cell anemia: demographic and social economic characteristics of patients and families of sickle cell anemia. J chronic dis 1985; 38:495-505.
6. De Gruchy, GC. "Clinical Hematology in Medical Practice" 4<sup>th</sup> edition CBS publishers Delhi India (Ed. Penington D, Rush B and Castaldi P) P 278, 1986.
7. World Health Organisation. Geneva. Hemoglobinopathies and allied disorders" Tech. Rep. Ser. 338; 5, 1966
8. Mwangemi, PM. sickle cell anaemia in adults at Kenyatta national hospital". M. Med Dissertation, University of Nairobi, 1977.
9. Allison, AC; "Protection afforded by sickle cell trait against subtertian malaria" BR. Med. J. 1:290, 1954.



10. Kendall, AG and Barr, RD; "hemoglobinopathies in Kenya"  
Trans. Roy. Soc. Med. Hyg. 67 (6): 770, 1973.
11. Aluoch JR, Aluoch LH. Survey of sickle cell anemia in Kenya. Trop Geogr Med. 1993 Mar; 45(1): 18-21.
12. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell anemia. Life expectancy and risk factors for early death. N Engl J Med 1994; 330:1639-1644.
13. Thomas AN, Pattison C, Seargent GR. Causes of death in sickle cell anemia in Jamaica. Bri Med J 1982; 285: 633-635.
14. Knight J, Murphy TM, Browning I. The lung in sickle cell anemia. Pediatr pulmonol 1999; 28:205-216.
15. Haupt HM, Moore GW, Bauer TW, et al. The lung in sickle cell anemia. Chest 1982; 81:332-337.
16. Powars D, Gladwin M G, Weidman JA, Odom - Maryon T, et al. Sickle cell chronic lung disease: Prior morbidity and risk of pulmonary failure. Medicine 1988; 67 : 66-76
17. Santoli F, Zerah F, Vasile N, et al. pulmonary function in sickle cell anemia with or without acute chest syndrome. Eur Respir J 1988; 12:1124-1129.
18. Koumboulis AC, Zar HJ, Hurlet-jensen, et al. Prevalence and reversibility of Lower airway obstruction in children with sickle cell anemia. J Pediatric 2001; 138:188-92.
19. Leong MA, Dampier C, Varlota L, et al. Airway reactivity in children with sickle cell disease. J Pediatr 1997; 131: 278-283.

20. Castele RJ, Stohl KP, Chester CS et al. Oxygen saturation in sleep in patients with sickle cell anemia. *Arch Intern Med* 1988;146:722- 725
21. Weil JV, Castro O, Malik AB, et al. Pathogenesis of lung disease in sickle cell anemia. *Amer J Respir Dis* 1993; 148:249-56.
22. Davie SC, Luce PJ, Winn AA, et al. Acute chest syndrome in sickle cell anemia. *Lancet* 1984; i: 36-38.
23. Poncz M, Kane E, Gill F. Acute chest syndrome in sickle cell anemia: Etiology and clinical correlates. *J Pediatr* 1985; 107:861-6.
24. Vichinsky EP, Styles LA, Colangelo IH, et al. Acute chest syndrome in sickle cell anemia: Clinical presentation and course. The cooperative study of sickle cell anemia. *Blood* 1997; 89:1787-92.
25. Castro O, Brambilla DJ, Thorington B, et al. The acute chest syndrome in sickle cell anemia: Incidence and risk factors. The cooperative study of sickle cell anemia. *Blood* 1994; 84:642-9.
26. Platt OS, Brambilla DJ, ROsse WF, Milner PF. Mortality in sickle cell anemia. *N Engl J Med* 1994; 330:1639-1644.
27. Vichinsky E, Styles L. Sickle cell anemia: Pulmonary complications. *Hematology Oncology Clin North Am* 1997; 10:1275-87.
28. Powars D, Weidman JA. Sickle cell anemia and major organ failure. *Hemoglobin* 1990; 14:573-597.
29. Aquino S L, Gamsu G, Fahy JV, et al. Chronic pulmonary disorders in sickle cell anemia: Findings at thin section CT. *Radiology* 1994; 193:807-811.

30. Sutton LL, Castro O, Cross DJ, et al. Pulmonary hypertension in sickle cell anemia. *Am J Cardio* 1994; 74:626-628.
31. Gray A, Anionwu EN, Davies SC, Brozovic M. Patterns of mortality in sickle cell anemia in the United Kingdom. *J Clin Pathol* 1991; 44:459-463.
32. Thomas AN, Pattison C, Serjent GR. Causes of death in sickle cell anemia in Jamaica. *Br Med J (Clin Res Ed)* 1982; 285:633-635.
33. Miller JG, Seargent GR. An assessment of lung volumes and gas transfer in sickle cell anemia. *Thorax* 1971; 26:309-315.
34. Young RC, Rachal RE, Reindolf CA, et al. Lung function in sickle cell hemoglobinopathy patients compared with healthy subjects. *N Engl J Med* 1988; 80: 509-514.
35. Femi- Pearce D, Gazioglu KM, Yu PN. Pulmonary function studies in sickle cell anemia. *J Appl Physio* 1970; 28:574 -577.
36. Jacob, G.F: "A study of survival rates in sickle cell anemia". *Brit. Med. J.* 1:738, 1957.
37. Gere CJ et al. Spirometric standards for healthy adult lifetime nonsmokers in Australia. *Eur Respir J* 1995; 8:773-782.
38. Hibbert ME, Lannigan A, Landau LI, Phelan PD. Lung function values from a longitudinal study of healthy children and adolescents. *Pediatr pulmonol* 1989; 7:101-109.
39. Dacie J V, Lewis S M. Investigation of the hemoglobinopathies from practical hematology. Longman Singapore publishers. 7<sup>th</sup> edition. 2001. Page 38

40. Cotes JE, Gilson JC. Reference values of lung functions in adults of European descent. Ann Occup Hyg 1967; 10:327-335.

APPENDIX 1

STUDY PROFORMA

DATE OF INTERVIEW -----

OUT/ INPATIENT NUMBER -----

STUDY NUMBER -----

NAME -----

AGE (YEARS) -----

SEX      1) MALE      2) FEMALE

HEIGHT -----

OCCUPATION -----

HISTORY ANY CURRENT ILLNESSES -----

PAST MEDICAL HISTORY INCLUDING ANY CRISES SUFFERED IN THE  
PRECEEDING ONE YEAR. -----

-----  
DRUG HISTORY

-----  
NUMBER OF ADMISSIONS

-----  
NUMBER OF TRANSFUSIONS  
-----

PHYSICAL EXAMINATION

GENERAL EXAMINATION -----

RESPIRATORY SYSTEM -----

ABDOMINAL EXAMINATION -----

CARDIOVASCULAR SYSTEM -----

MUSCULO - SKELETAL SYSTEM -----

CENTRAL NERVOUS SYSTEM -----

APPENDIX 2

DATA SHEET (SCA PATIENTS)

DATE OF INTERVIEW -----

OUTPATIENT NUMBER -----

STUDY NUMBER -----

NAME -----

AGE (YEARS) -----

SEX -----

HEIGHT -----

HEMOGLOBIN LEVEL -----

-OXYGEN SATURATION -----

-TLC -----

-RV -----

-FEV<sub>1</sub> -----

- FVC -----

-FEV<sub>1</sub>/FVC % -----

NUMBER OF PAINFUL CRISES IN THE PAST ONE YEAR -----

SEVERITY OF CRISIS;

NO MEDICAL ATTENTION GIVEN -----

TREATED AS OUT - PATIENT -----

ADMITTED TO HOSPITAL -----

NUMBER OF TRANSFUSIONS IN THE LAST ONE YEAR -----

DATA SHEET (CONTROLS)

DATE OF INTERVIEW -----

OUTPATIENT NUMBER -----

STUDY NUMBER -----

NAME -----

AGE (YEARS) -----

SEX -----

HEIGHT -----

HEMOGLOBIN LEVEL -----

- OXYGEN SATURATION -----

- TLC -----

- RV -----

- FEV<sub>1</sub> -----

- FVC -----

- FEV<sub>1</sub>/FVC % -----

NUMBER OF TRANSFUSIONS IN THE LAST ONE YEAR -----

### APPENDIX 3

#### SAMPLE SIZE ESTIMATION

The sample size was calculated using the formula below. (28)

$$N = \frac{(Z_{1-\alpha})^2 \cdot P(1-P)}{d^2}$$

N = Minimum sample size

$\alpha$  = level of significance=5%

P = Prevalence of sickle cell lung disease in SCA patients above 12 years

d = Degree of precision +/- 5

$(Z_{1-\alpha})^2 = 1.96$  (From tables of standard normal distribution) corresponds

2 to 95% confidence interval

The prevalence of sickle cell chronic lung disease is approximately 4% in

sickle cell anemia patients (10, 74). However a prevalence rate of 5% has

been used to calculate the sample size so as to accommodate the degree of precision.

$$\text{Therefore } \frac{1.96^2 \times 0.95 \times 0.05}{0.05^2} = 73$$

The minimum sample size of SCA patients required will be 73 (seventy three). One hundred and fifty will be recruited. Seventy five (75) SCA patients will be recruited and an equal number of normal age and sex matched controls



## APPENDIX 4 – CONSENT EXPLANATION

**Introduction;** My name is Dr Mukuha Michael. I am a postgraduate student pursuing a master's degree in internal medicine, University of Nairobi. The curriculum requires that I write a thesis, which entails collecting and analyzing data on various aspects of diseases. My research is on lung functions in patients with sickle cell anemia at KNH. To do this I will require to take a thorough history and do a physical examination on you. Further your lung functions will be assessed by way of spirometry which entails blowing air into a tube connected to a machine in the respiratory laboratory. For pulse oximetry a small clip will be attached to one of your fingers or earlobes just for a few seconds. These procedures are painless and do not cause any discomfort. I will draw 2mls (about a table spoonful) of blood for determination of hemoglobin level. This is a harmless procedure and will only be associated with some minor discomfort as I draw the blood and will only take a few seconds.

**Benefits** This study is intended to establish the pattern of respiratory function as well as the existence and the severity of lung dysfunction in patients with sickle cell anemia like you. This will help in planning of the care of patients with sickle cell anemia in the community. If you are found to have respiratory dysfunction you will be advised accordingly and will be referred to your primary physician for further follow-up.

**Risks** History taking, physical examination, spirometry and pulse oximetry have no risks. Taking venous blood for hemoglobin determination will only be associated with some minor discomfort. I will only use disposable sterilized needles and syringes and proper aseptic

techniques will be employed during blood sampling to ensure no risk to you.

**Participation.** Your participation in this study is purely voluntary. All information collected will be confidential. A written consent will be required from you before participation. You have a right to withdraw from the study at any stage without jeopardy to the current treatment that you are on. You have a right to know the results of all tests done. All costs will be borne by me.

**IN CASE OF ANY QUESTIONS, PLEASE CONTACT DR  
MUKUHA ON 0733801747**

APPENDIX 5

CONSENT FORM.

Consent by patient/ next of kin for participation in the study

I -----

Do hereby consent to participate in this study/research, the nature of which  
has been explained fully to me by Dr/ Mr. -----

I understand that the results of these tests shall be used for research work  
only and strict confidentiality shall be maintained at all times.

Date ----- Signed -----

I confirm that I have explained to the patient the nature of the study and  
tests to be done

Date----- Signed -----

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