TITLE

"CARDIOVASCULAR MANIFESTATIONS OF SICKLE CELL ANAEMIA IN PATIENTS OF 13 YEARS AND ABOVE AT THE KENYATTA NATIONAL HOSPITAL".

BY

PAUL OTIENO AYUO, MBchB, (NAIROBI) 1984.

A DISSERTATION SUBMITTED IN PART FULFILMENT OF THE DEGREE OF MASTERS OF MEDICINE IN MEDICINE UNIVERSITY OF NAIROBI 1990.

DECLARATION

THIS DISSERTATION IS MY ORIGINAL WORK AND HAS NOT BEEN PRESENTED FOR A DEGREE IN ANY UNIVERSITY.

SIGNED:.....

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THIS DISSERTATION HAS BEEN SUBMITTED FOR MASTERS OF MEDICINE IN MEDICINE EXAMINATION WITH OUR APPROVAL AS UNIVERSITY SUPERVISORS.

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SUMMARY

55 Sickle cell anaemia (SCA) patients were studied with a view to determining their cardiovacular status. Their ages were ranging between 13-27 years with a medium of 18.9 years. They comprised 27 males and 28 females. The main haemoglobin concentration was 8.5 ±1.4g/dL.

Haemoglobin level of 8-9g/dL seen in 30 patients was noted to confer the lowest incidences of exertional dyspnoea (40%) and palpitation (50%). This group also had lowest mean heart rate.

Systolic, diastolic and mean arterial blood pressures, Ejection fraction (EF) and differential fibre shortening (%D) were found to be directly related to haemoglobin concentration, whereas cardiothoracic index (CTI) and left ventricular dimensions had an inverse relationships to haemoglobin concentration.

The left venticular dimensions (LVD), Ejection fraction and differential fibre shortening were found to be normal in 80.9% of the patients indicating that the majority of patients with sickle cell anaemia at Kenyatta National Hospital have good cardiac functions.

INTRODUCTION AND LITERATURE REVIEW

James Herrick, a cardiologist in Chicago, published in 1910 the first generally accepted report on sickle cell disease (1). However, the phenotype of the disease has been known and accurately described by the Krobo tribe of Ghana for centuries (2). Earlier reports from North America suggestive of sickle cell disease date back to 1846 when a runaway slave with tall, lean features and autosplenectomy was described (3), and in 1898 a 32 years old black male with scars on anterior aspects of the legs and "no trace of spleen" at autopsy was described (3).

Following the report by Herrick (1), Washburn in 1911 reported a second case of a 25 year old woman (3) then Cook and Meyer in 1915 (4) and Mason in 1922 (5) reported two further cases. It was the latter who on summarising these first cases used the term "Sickle cell anaemia"(SCA) for the first time.

Vaso-occlusive and infarctive phenomenon in sickle cell disease were recognised first in 1924 by Graham describing wedge shaped areas of pulmonary infarction on chest radiographs (6). Wollstein and Kriedel in 1928 (7) and Steinberg in 1930 (8) noted small and medium sized pulmonary vessels containing thrombi with consequent fresh infarcts at autopsy. Later it was noted that infarcts were not confined to the lungs alone when in 1931 Yater and Mollari (9) and in 1934 Baird (10) recognised multiple infarctions of the kidneys and lungs.

Sickle cell disease (SCD) refers to all disease states where haemoglobin S (HbS) gene is present (11). When the patient is homozygous for HbS gene then the term sickle cell anaemia (SCA) is used, the term "trait" is used to designate all heterozygotes for an abnormal haemoglobin with HbA (2,3,11).

Haemoglobin 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 (12). In Africa the distribution runs in the equatorial belt from ocean to ocean including Madagascar (3,11,12). In Kenya the gene has a countrywide distribution with clusterings around the Lake Victoria basin and the coast province affecting mostly the Luo, Luhya, Nyika, Pokomo and Taveta tribes with an average frequency ranging from 0-30% (11,13-15).

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 a year (11). 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 1/2 year mortality rate of 5.26% making him conclude that SCA patients suffer early death (14). Jacob found that the chances of survival to adulthood were 14% in Uganda and 35% in Kenya in 1957 (16)

The clinical state of SCA is characterised by a "steady state" of chronic haemolysis, not different from other haemolytic anaemias, which is interrupted by crises (17). The crises tend to be more common in early life and becomes less frequent as adulthood is reached (18).

They can be classified into two broad groups viz vaso-occlusive and haematologic (19). The vaso-occlusive crisis is the thrombotic one whose clinical consequences are hand-and foot syndrome, recurrent painful and febrile crises, abdominal crises, hepatic crises, priapism, pulmonary and renal infarcts, etc., whereas haematologic crises encompasses:- a plastic crisis, megaloblastic crisis, haemolytic crisis and suquestration crisis if splenomegaly is present (19). It has been noted that the patients who get frequent painful crises have shorter life span than their counterparts getting less crises (20).

Factors influencing sickling of red blood cells in patients with SCA have been extensively studied in vivo and in vitro: HbS, HbC, HbD in the red blood cells and low oxygen tensions have been shown to promote sickling (12,21-30) whereas alpha-thalassaemia and haemoglobin F (HbF) inhibit sickling (31-34). Infections, fever, dehydration, acidosis or sudden cooling acting singly or in combination precipitate crisis in SCA (17).

The sickled red blood cells (RBC) are fragile, rigid and rapidly phagocytosed and hence responsible for the shortened survival of the circulating erythrocytes (19). Jaundice, marrow erythroid hyperplasia, nucleated RBC and high reticulocyte count in the peripheral blood are the consequences of haemolysis (19). Vascular occlusion, a consequence of elevated viscosity produced by the rigid sickled cells and their abnormal tendency to adhere to endothelial cells leads to hypoxia, which in turn initiates vasospasm, leakage of fluid and in turn more sickling - a vicious cycle leading to necrosis and infarcts (19,35,36), the final result of which is end organ damage.

The cardiovascular manifestation of sickle cell disease appears in the first description by Herrick who detected cardiac enlargement and precordial murmur (1). To date cardiovascular abnormalities are recognised as prominent part of the clinical picture of SCA, but the pathophysiologic mechanisms and clinical features are still not clearly worked out (37). Only a few studies of cardiac function in SCA appear in literature (38). Clinically the patients present with symptoms of exertional dyspnoea and palpitation reflecting diminished reserve of oxygen transport (37).

Cardiovascular examination usually reveals features of hyperdynamic circulation and cardiac enlargement marked by collapsing pulses, capillary pulsations hyperactive precordium, laterally displaced apical impulse. left parasternal heave loud HS 1, 11 S3 systolic murmur (ejection in quality but may be pansystolic to mimic mitral regurgitation murmur) (3,26,37,39). Blood pressures are typically low with no age rise as occurs in normal population the mechanism for which is unclear (40,41).

Left ventricular hypertrophy is almost a constant finding and right ventricular hypertrophy is common, the frequency of each finding depends on the method of investigation (3). Using echocardiography Gerry, Baird and Fortium noted increase in left ventricular dimensions (systolic and diastolic) left ventricular mass, interventricular septum and aortic root index in all their 23 adults with SCA (42). Similar findings including left atrium and less frequently right ventricular dilatation have been noted by other workers (37,43). These features have also been demonstrated in children of 0-15 years in Kenya (44).

Electrocardiographic (ECG) findings are non specific for SCA as they may be seen in other anaemias. Sinus rythm is a usual finding. P-R interval prolongation was noted in the first ECG on SCA patient in 1937 (45) and has since then been shown in several other studies with a frequency of 7-29% (26,39,46-48). Non specific ST-T changes are seen in 29-62% of patients (39,46,48). Evidence of left ventricular hypertrophy (LVH) is present in 18-59% and right ventricular hypertrophy (RVH) in 10-15% (26,39,46,49-51). ECG evidence of myocardial infarction is rare (46).

Radiographic examination of the chest almost invariably shows cardiac enlargment in 80-100% of cases (26,39,46,51), all chambers are enlarged confering a globur appearance to the cardiac silhoutte (37,38).

Autopsy studies have revealed cardiomegally by criteria of heart weight and left ventricular wall thickness. Average increase in heart weight by more than 25% of expected and left ventricular wall thickness of more than 1.5cm have been found (26,52). Other studies have shown bi-ventricular hypertrophy in 30-46% of hearts examined (46,52). Coronary heart disease and/or myocardial infarction are less frequently found at autopsy (38,53-55). In the few cases of myocardial infarction reported (54,55) there was no major coronary artery disease suggesting an alternative mechanism for the infarction. Haemosiderosis and cor-pulmonale are uncommon (52).

Patients with SCA have tachycardia at rest (43,46) with elevated cardiac index of 3.6-11.7 L/min/m^2 (47,50,56). In normal individuals resting cardiac output is elevated when the haemoglobin (Hb) is 7 g% or less as opposed to SCA where cardiac output has been found to be elevated with haemoglobin concentratation of 9-10g% (57).

Leight, Snider, Clifford and Hellems did not demonstrate any relationships between cardiac index and haemoglobin level but found greatest cardiac output to occur in patients with lowest haemoglobin concentration (47).

Response to exercise is abnormal in SCA patients. On maximal exercise the heart rates of SCA were found to be lower than those of healthy controls and cardiac output only doubles whereas in normals it tripples (3).

Left ventricular ejection fraction rises, but to a lesser extent than controls and left ventricular end diastolic volume (LVEDV) falls on exercise, this being related to the impaired cardiac output response (58,59). Whereas the role of myocardial ischaemia in limiting excercise is unclear ECG evidence of ischaemia during exercise has been reported in 15% of 47 patients aged 5-18 years (59). Such patients tended to have falling ejection fraction on exercise (58).

Literature review shows that SCA is a disease which considerably shortens lifespan (11,14,15,19) apart from its social and economic implications. The cardiac and pulmonary complications are major contributors to its morbidity and mortality in the primes of ages. Studies on SCA in our set up are not exhaustive. Cardiovascular functions have been done on paediatric age group (44). In adults only radiographic and electrocardiographic features have been studied (14). This work is an attempt to find out and document the prevalence and severity of cardiovascular complications in SCA as there is paucity of literature regarding the same in our set up.

AIMS AND OBJECTIVES

1. To determine the cardiovascular manifestations of sickle cell anaemia in adults in steady state at Kenyatta National Hospital.

2. To determine the frequency of such manifestations.

3. To determine cardiovascular status by:

   i) physical examination (concentrating on cardiovascular, system);

   ii) chest radiography;

   iii) electrocardiography;

   iv) echocardiography;

   v) to correlate the data obtained with age, sex and haemoglobin concentration.

4. To make recommendation on possible areas of future research.

PATIENTS AND METHODS

PATIENTS

Patients for this study were drawn from the Haematology clinic of Kenyatta National Hospital. Only the patients who gave informed consent and met the inclusion criteria were recruited into the study. All patients seen had been diagnosed as having sickle cell anameia (SC.A) by Cellulose Acetate paper Electrophoresis (C.A.P.E). 55 patients qualified.

Inclusion criteria

1. Age of 13 years and above

2. Having Haemoglobin S(HbS) or Haemoglobin SF (HbSF) bands on cellulose Acetate paper Electrophoresis (CAPE) at PH of 7.9 - 8.9.

Exclusion criteria

1. sickle cell crisis at the time of investigations. Sickle cell crisis was defined as a definate change in clinical symptoms requiring emergency management (18,49).

2. Blood transfusion within the previous three months.

3. Presence of intercurrent illness - acute or chronic (e.g. malaria, respiratory tract infection, rheumatic heart diseases.)

4. History of cigarette smoking.

METHODS

After noting personal information (age, sex etc) and brief history the following were done:-

i) Respiratory rate and radial pulse rate were each counted over one full minute with patient seated and relaxed. In addition the character and regularity of the pulse were noted.

ii) Blood pressure was measured with the patient seated comfortably (at least for 5 minutes) not having taken coffee in the previous half hour. A mercury sphigmomanometer with a standard 12.5cm cuff was used according to the protocol recommended in the American Heart Association (A.H.A.) a report (60).

iii) A detailed physical examination was carried out with specific reference to the cardiovascular system. (C.V.S.)

iv) 2 mls. of blood was drawn from the cubital vein using a torniquet, sterile neddle and syringe after skin preparation by surgical spirit. The blood was placed into a bottle with Ethylenediaminotrichloroacetic acid (EDTA) for haemoglobin estimation. Haemoglobin concentration was estimated by using " COULTER COUNTER MODEL S-5" In the Department of Medicine University of Nairobi.

v) Postero-anterior chest radiographs were taken in full inspiration (not necessarily in the day of interview) and the cardiothoracic index (C.T.I) was calculated according to the recommendation by Jefferson and Rees (61).

vi) 12 lead resting electrocardiograms were recorded using Siemens ' CARDIOSTAT -1" machine after patients were examined. Each subject was recorded relaxed lying flat (supine) on a couch not having smoked or taken coffee within the previous half hour.

vii) Using ALOKA ECHOCARDIOGRAPH SSD-725 and a $2MH_z$ transducer, echocardiography was carried out on appointment date after the interview. The patients were placed in a left lateral position at about 30° and the transducer positioned 3-4 cm from left sternal border at 3rd or 4th intercostal space from which a strong mitral value echo was visualised, with the transducer directed posteriorly and medially, then the beam directed slightly laterally and inferiorly away from the mitral valve until a plane is found in which motion of the interventricular septum and posterior left ventricular wall is noted. Then the left ventricular minor axis measurement were done in the following manner:-

a) Left ventricular dimension in diastole (LVDd) - at the Q wave of a simultaneously displayed electrocerdiogram (ECG).

b) Left ventricular dimension is systole (LVDs) - at the time of maximum anterior motion of the posterior left ventricular wall.

c) Differential fibre shortening (%D) was calculated from the formular $\frac{LVDd - LVDS}{LVDd} \times 100$ (64,65)

d) Left ventricular ejcection fraction (EF%) was automatically calculated from the Echo machine.

STUDY DESIGN AND STATISTICAL CONSIDERATIONS

The study was carried out in a period of seven months from May to November (inclusive) of 1989. It was designed to be a descriptive study and due to anticipated material and logistic problems, and time limitation a target of 50 patients was set to be the sample size. However 55 patients were entered into the study. They make up 19.6% of 280 sickle cell anaemia (SCA) patients currently booked at the adult haematology clinic (Dr.J.R. Aluoch personal communication). The results were subjected to Chi squere, students t tests and Analysis of variance (ANOVA) where appropriate.

ETHICAL CONSIDERATIONS

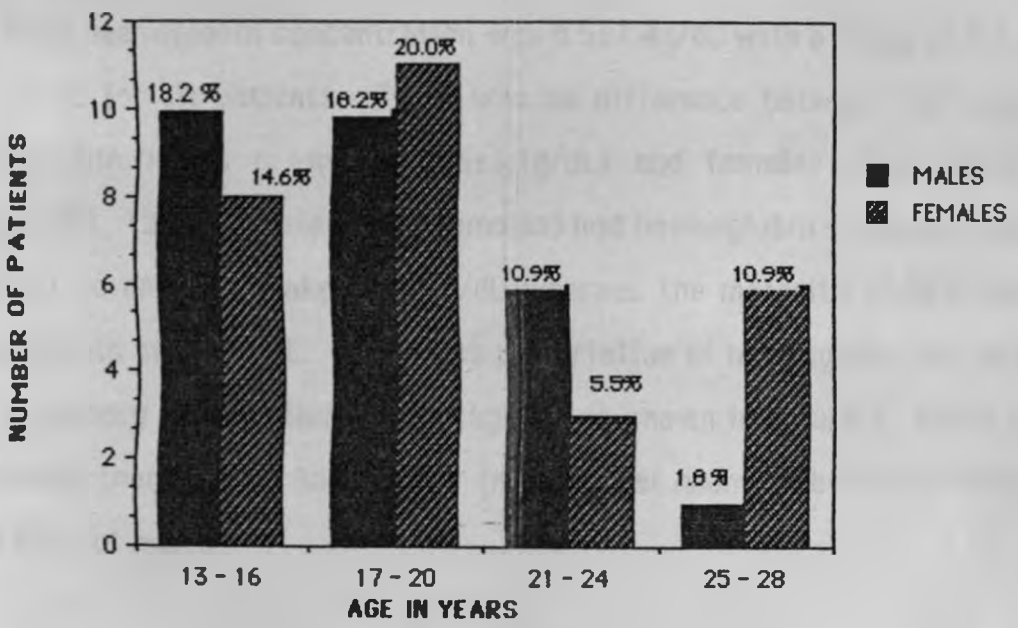
The proposal for this study was presented to the Ethical and Research Committee and permision was granted before commencement.

RESULTS

DEMOGRAPHIC DATA

55 consecutive patient with SCA were enrolled into the study. Their ages ranged from 13 years to 27 years with a mediam age of 18.9 years. They comprised 27 males (median age 18.6 years) and 28 females (median age 19.4 years). The male to female ratio was 1:1 and there was no stastical difference between the mean ages of males (17.6±3.4 years) and females (19.6±4.2 years) (observed difference was less than twice the standard error of difference) (2SE=2.06). Figure1 depicts the age and sex distribution where it is seen that majority (38.2%) of the patients are confined to 17-20 years age group thereafter the number falls steadily (both sexes) till 25-28 years age group when the females far outnumber the males (10.9% vs 1.8%).

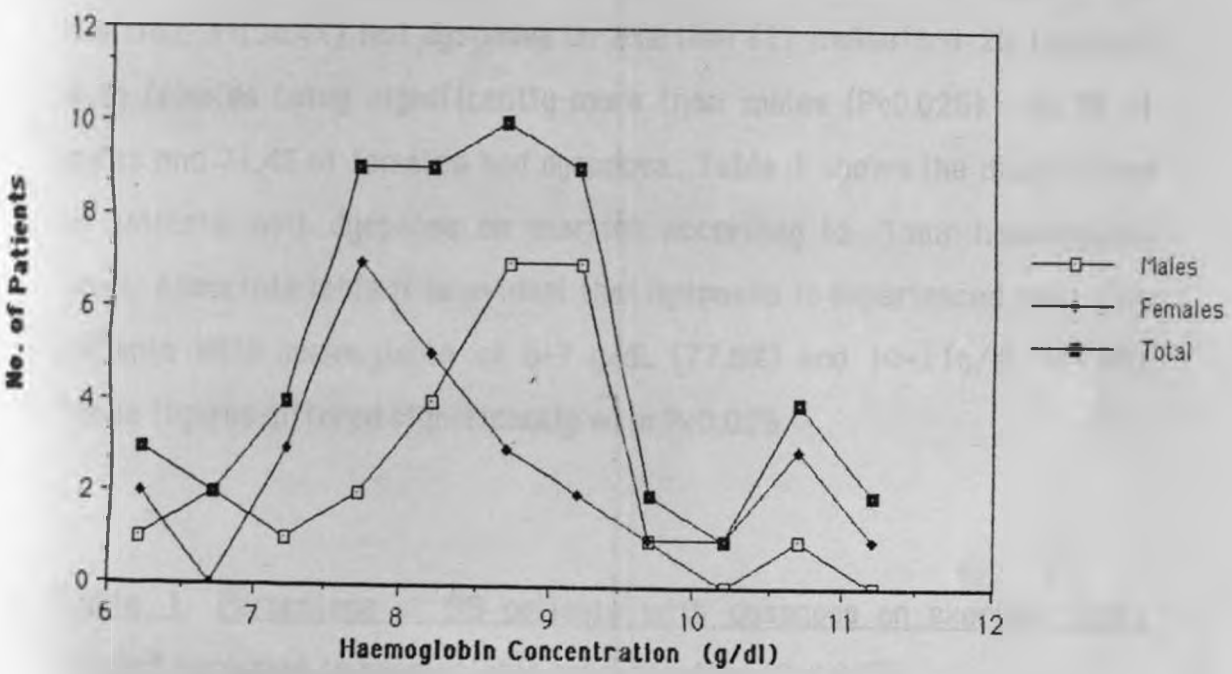
Fig 1. Bar chart showing age and sex distribution Of 55 patients with Sickle Cell Anaemia (SCA)



HAEMOGLOBIN CONCENTRATION.

The mean haemoglobin concentration was 8.5±1.4g/dL with a range of 6.0 - 11.1 g/dL for all patients. There was no difference between the mean haemoglobin levels of males (8.6±1.1g/dL) and females (8.4±1.7gldL) (2SE=0.78). 12.7% (2 males and 5 females) had haemoglobin - concetration of equal to and more taken 10.0 g/dL whereas the majority (54.6%) had haemoglobin of 8-9 g/dL. There was no variation of haemoglobin and age. The frequency distribution of haemoglobin is shown in fugure 2, where it is evident that females have higher frequency at haemoglobin level lower than that of males.

FIG 2. Frequency distribution of Hb
Concentration of 27 males and 28 females (55 Patients)



DYSPNOEA

4 patients (7.3%) gave a history of dyspnoea grade IV. They were all females and had haemoglobin concentrations which were not distinctly different from others (9.2, 7.8,10.6 g/dL). They also had dyspnoea an exertion. 31(56.4%) had dyspnoea on exertion (11 males and 20 females) with females being significantly more than males ($P<0.025$). 40.7% of males and 71.4% of females had dyspnoea. Table 1 shows the distribution of patients with dyspnoea on exertion according to their haemoglobin level. From this table it is evident that dyspnoea is experienced mostly by patients with haemoglobin of 6-7 g/dL (77.8%) and 10-11g/dL (71.4%). These figures differed significantly with $P<0.025$.

Table 1 Percentage of 55 patients with dyspnoea an exertion (DOE) grouped according to haemoglobin concentration ($P<0.025$)

HAEMOGLOBIN g/dl	NO. PATIENTS IN Hb GROUP	NO. OF PATIENTS WITH DOE	%AGE OF PTS WITH DOE
6 - 7	18	14	77.8
8 - 9	30	12	40.0
10 - 11	7	5	71.4
TOTAL	55	31	56.4

PALPITATIONS

37(67.3%) of the patients complained of palpitations. 13 were males and 24 females who dominated significantly. ($P<0.005$) that is 48.2% of all males and 85.7% of all females. Table II shows the distribution of patients with palpitations according to their haemoglobin concentrations. It has a similar pattern to table I thus patients with haemoglobin of 8-9g/dL showing least incidence (50%) of palpitations. The differences were significant of $P=0.01$.

Table II Percentage of 55 patients with palpitation grouped according to haemoglobin level. ($P=0.01$).

HAEMOGLOBIN LEVEL g/dl	NUMBER OF PATIENTS IN Hb. GROUP	NUMBER OF PATIENTS WITH PALPITATIONS	PERCENTAGE OF PATIENTS WITH PALPITATIONS
6 - 7	18	16	88.8
8 - 9	30	15	50.0
10 - 11	7	6	85.7
TOTAL	55	37	67.3

HEART RATE

The mean heart rate was 82.2 ±11.4 beats per minute with a range of 50-110 beats per minute. The mean heart rate for males (79.6±12.4 beats per minute) did not differ significantly from that of females (84.8±9.9 beats per minute (2SE=6.08). One patient (1.6%) - male had sinus bradycardia (50 beats per minute) of undetermined cause whereas 5(9.1%) had tachycandia at rest. Haemoglobin level of 8.9 g/dL conferred the least mean heart rate . Table III shows mean heart rates according to haemoglobin level and one stage analysis of variance showed non dignificant relationships. Table IV shows inverse relationship of mean heart rates and age from 17 years upwards. Analysis of variance showed this relationship to be significant.

Table III: The mean heart rate, sustolic blood pressure, diastolic blood pressure and mean artenal pressure of 55 patients shown against haemoglobin level.

Hb g/dl	NO. OF PTS WITH Hb	MEAN HEART RATE ± ISD $BMIN^{-1}$	MEAN SYSTOLIC BP ± ISD (mm Hg)	MEAN DIASTOLIC BP ± ISD (mm Hg)	MEAN MAP ± ISD (mm Hg)
6 - 7	18	82.6 ± 8.0	114.4 ± 11.1	62.8 ± 8.4	79.7 ± 8.5
8 - 9	30	81.0 ±13.0	115.0 ± 10.3	63.7 ± 12.1	80.4 ± 7.8
10-11	7	86.4 ±11.9	115.7 ± 5.4	73.6 ± 7.5	87.3 ± 6.2
TOTAL	55	83.4	115.05	66.67	82.5
P		>0.05 N.S.	<0.05 S	<0.05 S	<0.05 S

Key

$BMIN^{-1}$ - Beats per minute

g/dl - grams per decilitre

mmHg - Millimetres of Mercury

NS - Notsignificant

S - Significant

1SD - One standard deviation

BLOOD PRESSURE

1. SYSTOLIC BLOOD PRESSURE

The mean systolic blood pressure was 114.9±9.9 mm Hg with arrange of 100-140mm Hg. These was significant difference between the mean systolic blood pressures of males (110±8.8 mmHg) and females. (119.6±8.7 mmHg) (2SE=4.74). 1 patient (1.8%) female had a systolic blood pressure of 140 mmHg. The mean systolic blood pressure according to haemoglobin levels are shown in table III, and it is evident that the mean systolic blood pressure is directly related to the haemoglobin level significantly (ANOVA). However the correlation between the two parameters for all patients was very low. (Correlation coeffient of +0.088, and Regression coefficient of +0.722). The age group 21-24 years had the lowest mean systolic blood pressure (108.3±7.1 mmHg). There was significant difference (ANOVA) between mean systolic blood pressures and age as shown in table IV.

2. DIASTOLIC BLOOD PRESSURE.

The mean diastolic blood pressure was 64.6± 10.9 mmHg and the range was 40-90mmHg. Males (61.5±9.6 mmHg) had lower diastolic than females (67.7±11.3mmHg) (2SE=5.68). One female (1.8%) had a diastolic pressure of 90 mmHg whereas 20% (7 males; 4 females) had pressures of less than 60 mmHg. The mean diastolic pressure is directly related to haemoglobin level significantly (ANOVA) as shown in table III.

There was positive correlation between haemoglobin and diastolic blood pressures for all patients (r=+0.25, regression Coefficeint 2.22). The mean diastolic blood pressure differed according to age groups significantly (ANOVA) as shown in table IV. Highest mean diastolic pressures were noted in 25 - 28 year (69.3 mmHg) and 13-16 year (67.2 mmHg), age groups.

Table IV: Mean heart rates, sustolic blood pressure, diastolic blood pressure and Mean arterial pressure (MAP) of 55 patients shown against age group.

AGE (YRS)	NO. OF PTS IN AGE GROUP	MEAN HEART RATE ± ISD ($BMIN^{-1}$)	MEAN . SBP ± ISD (mmHg)	MEAN. DBP ± ISD (mmHg)	MEAN MAP±ISD (mmHg)
13-16	18	82.7±12.2	117.8±10.2	67.2±11.7	83.7±10.4
17-20	21	84.4±10.8	113.1±10.1	60.0±10.9	77.3± 9.3
21-24	9	80.7±11.7	108.3± 7.1	66.7± 8.7	80.3± 5.6
25-28	7	76.4±11.2	121.4± 7.0	69.3± 8.4	86.3± 5.9
TOTAL	55	81.06	115.60	65.8	81.9
P		<0.05 S	<0.05 S	<0.05 S	<0.05 S

NOTE: $BMIN^{-1}$ - Beats per minute . ISD - One standard deviation
S - Significant . MmHg - Millimetres of Mercury

MEAN ARTERIAL PRESSURE (MAP)

The mean MAP was 81.04±9.3 mmHg with males having significantly lower values than females (2SE=4.6) 77.3±9.7 mmHg compared to 84.7±9.0 mmHg. In table III it is seen that MAP is directly related to haemoglobin level and one stage analysis of variance confirms this to be significant. MAP is also directly related to age from 17 years onwards as depicted in the last column of table IV. One stage analysis of variance shows that MAP is dependent on age.

3. CHEST RADIOGRAPHS

Of the 55 patients, 39(22 males :17 females) had good quality chest radiographs which were analysed; 8 had poor quality films: 6 had films which could not be traced and 2 did not present themselves for radiography. Cardiothoracic index (CTI): mean was 0.52±0.03 with range of 0.42-0.61. Males (0.53±0.04) had higher index than females (0.51±0.03) significantly (2SE=0.02). Cardiomegally (CTI>0.5) (61) was noted in 64.1% whereas 23.1% had normal chest radiographs.

The rest had various abnormalities with (12.8%) or without normal cardiac shadow:- features of congestive heart failure 46.2%, infection (bronchopneumonia, old tuberculosis, nonspecific) 10.3%, and filling of pulmonary bay 25.7%

There was no consistent relationships of cardiothoracic index with age $P>0.05$ whereas it was significantly inversely related to haemoglobin level shown in Table V. ($P<0.05$). The correlation of haemoglobin and Cardio-thoracic index was found to be low ($r=-0.39$) for all patients as shown in scatter diagram Fig.3.

Table V: Mean Cardiothoracic indices of 39 patients according to their haemoglobin levels.

HAEMOGLOBIN LEVEL g/dL	NUMBER OF PATIENTS WITH ANALYSED CXR	MEAN CTI ± ISD
6 - 7	12	0.54 ± 0.03
8 - 9	21	0.52 ± 0.03
10 - 11	6	0.50 ± 0.01
TOTAL	39	0.52
		P< 0.05
		S

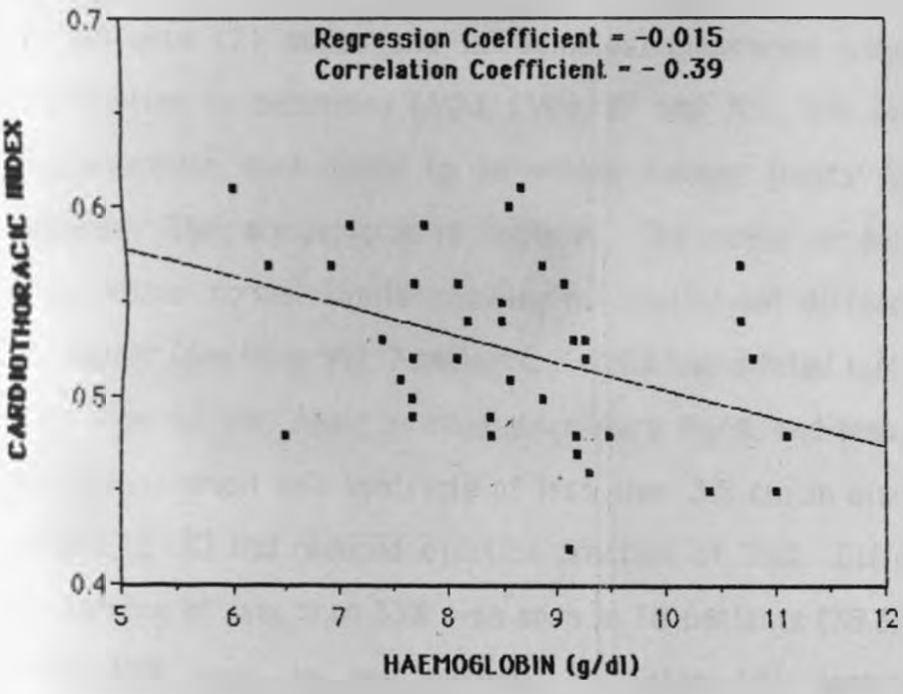
NOTE:

CXR - chest radiograph (chest X-ray)

ISD - one standard deviation

S - significant P-value

FIG 3. A SCATTER Diagram: Cardiothoracic Index of 39 Patients against Hb Concentration



ECHOCARDIOGRAPHY

47 patients (21 males and 26 females) underwent Echocardiographic examination to determine LVDd, LVDs, EF and %D. The means of these measurements were found to be within normal limits for all the 47 patients. They are depicted in table VI. The means for both sexes were also within normal limits showing no statistical difference for each parameter (see table VI), 7 patients - 14.9% had dilated left ventricles of more than 5.7 cm, their haemoglobins were 9g/dL and less, and 1(2.1%) had a very small left ventricle of less than 3.5 cm in diastole. Only 1 patient (2.1%) had reduced ejection fraction of 39%. Differential fibre shorterning of less than 33% was seen in 18 patients (38.3%) - the least being 15% seen in one patient. Table VII depicts the mean echocardiographic parameters according to haemoglobin and it is noted that LVDd, and LVDs are inversely related to haemoglobin level, whereas EF and %D are directly related but not to a significant level by statistical test.

Table VI: Range and means of Echo parameters of 47 patients and means of these parameters in males and females separately.

ECHO MEASUREMENT	ALL 47 PATIENTS RANGE	MEAN±ISD	21 MALES MEAN ±ISD	26 FEMALES MEAN ±ISD	25.E
LVDd (cm)	3.3 - 6.6	5.06±0.68	5.14±0.61	5.00±0.73	0.4 NS
LVDs (cm)	2.0-4.9	3.30±0.57	3.34±0.57	3.26±0.57	0.34 NS
EF %	39-87	71.3±7.8	71.2±4.6	71.3±9.8	4.32 NS
%D	15-50	34.7±6.8	34.8±6.8	34.6±6.9	4 NS

Key

Echo - Echocardigraphy

EF - Ejection fraction

%D - Differential fibre shortening

LVDd - Left ventricular dimension in diastole

LVDd - Left ventricular dimension in systole

SE - Standard error of the difference

NS - Not significant

ISD - One standard deviation

Table VII: Mean Echo parameters of 47 patients according to haemoglobin level

Hb LEVEL g/dl	NO. OF PTS IN HAEM. LEVEL	MEAN LVDd ± ISD (cm)	MEAN LVDs ± ISD(cm)	MEAN EF% ±ISD	MEAN%D ±ISD
6 - 7	16	5.27±0.41	3.49±0.54	69.4±11.6	33.5±7.9
8 - 9	25	5.13±0.65	3.33±0.50	71.3±7.4	34.6±5.9
10 - 11	6	4.33±0.57	2.65±0.52	76.1±7.0	38.6±6.6
TOTAL	47	4.91	3.16	72.3	35.6
P		NOT SIGNIFICANT P>0.05	NOT SIGNIFICANT P>0.05	NOT SIGNIFICANT P>0.05	NOT SIGNIFICANT P>0.05

ELECTROCARDIOGRAPHY. (ECG)

52 patients had good quality ECG tracings which were read. They comprised 25 males and 27 females. 76.9% of the patients had abnormal ECGs and a total of 62 ECG abnormalities were seen. There was no relationship between ECG abnormality and haemoglobin level. Table VIII summarises the distribution and types of ECG abnormalities seen.

Table Viii: Summary of Electrocardiographic findings in 52 patients with sickle cell anaemia

PTS	NO. OF PTS DONE ECG	NO. OF PTS WITH ABNORMAL ECG	NO. OF PTS WITH NORMAL ECG	NO. OF ECG ABNORMALITIES	EGG ABNORMALTIES				
					LVH	RVH	LAE	ST-T	P.R PROLONG
MALES	25	22	3	34	16	2	5	7	4
FEMALES	27	18	9	28	12	2	6	5	3
TOTAL	52	40	12	62	28	4	11	12	7
%	100	76.9	23.1	100	45.2	6.5	17.7	19.4	11.3

KEY

LVH - Left Ventricular hypervoltage
RVH - Right Ventricular hypervoltage
LAE - Left atrial enlargement
ST.T-ST Segment, T wave changes
P.R PROLONG - PR prolongation
ECG - Electrocardiography
PTS - patients

DISCUSSION.

AGE AND SEX DISTRIBUTION

This study shows that most patients (71%) with sickle cell anaemia (SCA) attending the haematology clinic are aged 20 years and less. The oldest seen were 27 years. Two earlier studies at Kenyatta Naitonal Hospital (KNH) had shown the same pattern of age distribution (14,69), which was attributed to: 1) high mortality rate in young SCA patients and ii) the general population distribution in the country. The two previous studies and the current one were carried out in an urban setup and the results on age distribution cannot be projected to represent that of all SCA patients in the rural areas. Another notable point in the present study which is not covered by the advanced reasons above, is that above 25 years females outnumber males six times (10.9% against 1.8%). This discrepancy cannot be explained by this study.

SYMPTOMATOLOGY. (DYSPNOEA AND PALPITATION)

It is generally agreed that candiorespiratory complaints in SCA are frequent and due to diminished reserve of oxygen trasport system (37,47,50). Exertional dysponea and palpitations have been cited and dyspnoea at rest makes the picture more complicated. However, the non-specificity of these symptoms renders them of little analytical value (37).

In this study 7.3% ofthe patients had dyspnoea at rest, but investigations did not separate them from the rest. Of 56.4% who had exertional dyspnoea, females were more than males significantly, a factor which cannot be explained by this study on the basis of haemoglobin concentration,- there was, no male - female haemoglobin difference or hemoglobin variation with age in females contrary to the general expectation. The same applies to palpitation.

If these symptoms are dependent on impaired oxygen transport alone, then we expect highest incidence in patients with lowest haemoglobin and vice versa. However, this study shows that the least incidences of 40% and 50% exertional dyspnoea and palpitation respectively occured at haemoglobin level Of 8-9 g/dL and not 10-11 g/dL. This could be due to either chance playing a major role as these symptoms are subjective or the fact that the Kenyan type of SCA being the severe type (Central African Republic type), the patients who had haemoglobin level above 10g/dL were having poor quality haemoglobin pigment. The narrow range of haemoglobin stratification could not be responsible for this observation as the haemoglobin groups which had comparable incidences were widely spaced (6-7 and 10 -11 g/dL).

HEART RATE:

The heart rate of a normal individual is 60 to 100 beats per minute (62). Above 100 beats per minue is tachycardia Tachycardia at rest is noted in most patients with SCA (43). The findings of this study are not in agreement with that general belief as only 9% of the patients had tachycardia at rest, which is still less than 27% found by USzoy (46). Literature reviewed did not have any data on sinus bradycardia seen in 1.8% in the present series.

Comparisons of heart rate of populations staying in different geographical areas is not in order as factors like altitude have to be put into consideration. Sample sizes is another source of discrepancy. Whereas the mean heart rate in the present series was normal (82.2±.4 beats per minute) the lowest (71.4 beats per minute) was noted in haemoglobin of 8-9 g/dL the same groups that had least incidence of palpitation and exertional dyspnoea. This finding could support the argument that questioned the quality of haemoglobin in patients who had a concentration of 10-11 g/dL as regards incidence of exertional dyspnoea and palpitations.

Heart rate is inversely related to age in normal people (66,67) , a trend which is also seen to a significant level in SCA patients above 17 years in the present study. Taking the normal patients of Okwera (66) and Wanene (67) as historical controls, the finding of higher mean heart rates in SCA patients supports the earlier reports by Balfour et.al (43).

BLOOD PRESSURE

The blood pressure in sickle cell anaemia patients is low and demonstrate no age rise as is seen in normals (40,41,68). Hypertension is rare, even in the presence of renal disease (41). The mechanisms responsible for the low blood pressures in sicklers are unclear, but some workers have proposed, renal medullary ischaemia and prostaglendin secretion (68), and renal tubular defects causing increased sodium and water loss (40). Both systolic and diastolic blood pressures have been found to be lower in sickle cell anaemia patients than normal controls. Wanene (67) in a study of normal rural Kenyan population found that the blood pressure rises with age steeply up to 20 years then gradually. The present study shows that blood pressure of sicklers do not rise with age and are lower than those of normal Kenyans (67), of comparable age groups, especially from 17 years and above. These findings support those of earlier workers (40,41,68)

Literature on relationship of blood pressure and haemoglobin concentration in sicklers is scanty, and from this study it is noted that blood pressure is directly related to haemoglobin concentration to a significant level. This relationship may arise partly due to hypoxic vasodilatation due to anaemia in these patients, and supports the role of subjectivity in the incidence of symptoms (see dyspnoea and palpitation) as opposed to quality of haemoglobin pigment.

CHEST RADIOGRAPHS

Compensatory hypertrophy and dilatation from increased venoes return secondary to anaemia account for the cardiomegally seen in chest radiographs of sickle cell anaemia patients (38). The cardiac shadow has been described as globular (37,38) and pulmonary artery and left atrial enlargement cause filling of the pulmonary bay (37). In the present study cardiomegally was noted in 64.1% of patients which is slightly lower than but comparable to the findings of 70-100% in different series including a study at Kenyatta National Hospital by Mwangemi (14,26,46,50), but age differences and sample sizes could account for this discrepancy. 25.7% had filling of pulmonary bay. That cardiomegally in sicklers is due to anaemia means that the cardiothoracic index would be inversely related to haemoglobin level a feature which was seen significantly in the present study as in earlier studies of Serjeant (3) and Ng et. al (39).

Vascular redistribution suggesting heart failure is uncommon (38), but in the present series it was seen in 46.2% of the radiographs. This could be due to a good number of our patients having very low haemoglobin levels (32.7% had haemoglobin of below 8/dL).

ECHOCARDIOGRAPHIC FINDINGS

Echocardiographic findings in different studies have shown evidence of left ventricular dysfunction in children (44,72) and not adults (38,42,72). In the present study it is demonstrated that the mean left ventricular dimensions were within normal limits and are comparable to those of normal adults of Fortium et .al (65). The present series has a lower mean age (18.6 years compared to 22.4 years) and if the age discrepancy could be corrected one may assume that our patients really had higher measurements. Results obtained however, show that only 14.9% had dilated left ventricles as opposed to the finding of universally enlarged hearts by Gerry et-al (42). The ejection fraction (EF) is a measure of pump performance of the heart and has been widely used as an indirect indicator of myocardial perfomance and together with differential fibre shortening (% D) can be used to separate normal cardiac function from congestive heart failure (65,70). In normal people %D has been found to be 33% (65) and ejection fraction 59-67% with none being less than 51% (65,71) by angiography. Our patients had mean %D of 34.7% and EF of 71.3% (higher than the normals of Fortium et.al) (65), therefore normal left ventricular functions as asessed by echocardiography. Only one patient demonstrated depressed left ventricular functions by having both EF and %d. below normal (EF of 39% and % D of 15%). The low %D in the other (17) patients with normal EF may be regarded as errors.

This study reveals that the left ventricular parameters measured; Left ventricular dimensions (inversely), EF and % D (directly) are related to haemoglobin levels. This agrees with the general observation that anaemia plays a major role in cardiovascular derangements in sicklers. Such a relationship, however, has neither been noted in children with sickle cell anaemia (44), 72) nor recorded in adults.

ELECTROCARDIOGRAPHIC FINDINGS

ECG abnormalities have been found with different frequencies in patients with sickle cell anaemia (26, 39,46-51) despite lack of specificity. Overall in the present study, 76.9% of the ECGs were found to have at least one abnormality, a frequency comparable to 78% found by Uzsoy (46). The ECG abnormalities have been found with less frequency in children (44).

Increased vagal tone compensating for the prolonged hypoxia (anaemia) is responsible for P-R prolongation (26), occuring in 7-29% of ECGs. In the present study this abnormality was seen in 11.3% of the patients comparing well with 10% noted by Lind say (37).

Non specific ST-T changes are seen in 29-62% of cases from different series (39,46,48). This was initially thought to be due to ischaemia and scarring of myocardium due to clogging of vessels by sickled red cells until its occurence in normal people was realised (66,73).

S-T elevation and T wave inversions beyond V3 is now recognised as the "Juvenile pattern" and occurs in 35 - 37% of normal Africans (66,73), though Wanene (67) did not find the T-wave inversion beyond v3 after 15 years of age.

From the foregoing one expected a high incidence of ST-T segment changes in our patients - they being Africans. Unexpectedly it was noted in only 19.4%. The small sample size in the presence study could account for this low figure.

The incidence, in the present study, of Left ventricular hypervoltage (45.2%) and right ventricular hypervoltage (6.5%) are comparable to 18-59% and 10-15% respectively in earlier studies (26,39,46,44-51), but - not 70% as found by Mwangemi (14). The lowest incidence (71.4%) of ECG abnormality occured at haemoglobin of 8-9gldL. Considering that the lowest incidences of dyspnoea and palpitation and lowest mean heart rates occured at this haemoglobin level; this finding supports the argument that there was poor haemoglobin quality in patients with haemoglobinn concentration of 10-11g/dl. However, other parameters do not support this theory.

CONCLUSIONS AND RECOMMONDATIONS

This study shows that sickle cell anaemia patients in our set up have fairly good cardiovascular functions.

It is also noted that the findings are fairly comparable to those of other sicklers studied elsewhere except for the undermentioned: tachycandia at rest which has been described in most patients with sickle cell anaemia was noted in only a small proportion of patients in this study, our radiographic findings tended to over suggest congestive cardiac failure which was not noted clinically: and cardiomegally as diagnosed by echocadiography has been termed as univeral whereas our values could not support this universality. In conclusion, this study has elicited differences and similarities of SCA patients at Kenyatta National Hospital and those elsewhere. The differences can be explained on 1) chance occurences and 2) the severity of SCA type in Kenya and 3) geographical differences.

Recommendations are:

1. RBC morphology and haemoglobin types should be included in future studies of similar nature to outline the role of these in functional difference.

2. Controlled study of anaemic patients (nonSCA), and normals should be carried out to authenticate the derangements noted in the present study.

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APPENDIX I

DATA COLLECTION FORM

GENERAL INFORMATION

Date _____ Age (yrs) _____

Study No_____ Sex _____

Unit No_____

Name _____

CLINICAL DATA

	Yes	No
Dysponea at rest	___	___
On exertion	___	___
Palpitation	___	___

Pulse rate (per minute)_____

Blood pressure (mmHg)_____

Liver _____ Spleen_____ Below costal margin

Cardiac murmus Systolic _____ Diastolic _____

Apex beat _____

APPENDIX I

LABORATORY DATA

Haemoglobin (g/dL) _____

Cardiothoracic Index _____

	YES	NO
RVH	_____	_____
LVH	_____	_____
RAE	_____	_____
LAE	_____	_____
P-R - PROLONGATION	_____	_____

LVD Diastole_____ Systole _____

EF _____

%D _____

APPENDIX II

CRITERIA

In this study the following will be taken as normals or reference points for the various parameters.

1. Respiratory rate 14 - 18/min (62)

2. Heart rate 60 - 100/min (62)

3. Blood pressure: systolic 100-140,
   diastolic 60 - 90 mmHg (60)

4. Cardiothoracic ratio: upper limit 50%, index 0.5 (61)

5. (63) LVH: $SV_1 + RV_6 \geq 36$ mm.
   RVH: $RV_1 > SV_1$; q^R pattern in VI
   LAE: PII/VI $\geq$ 0.12s
   RAE: PII/III/aVF $\geq$ 0.25 mV.
   P-R internal 0.12 - 0.20s
   QRS duration 0.04 - 0.10s

6. (64)
LVPW	0.6 - 1.1 cm
LVID	3.5 - 5.7 cm
IVS	0.6 - 1.1 cm
RVD	0.7 - 2.3 cm
LAD	1.9 - 4.0 cm