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Cardiac Dimensions and Functional Parameters in Nigerian Children with Homozygous Sickle Cell Anaemia Using Echocardiography

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Abstract

Background: Sickle cell anaemia (SCA) is the most common and burdensome inherited disease affecting children in Africa. Nonetheless, there remains a paucity of literature from Nigeria about its effects on cardiac dimensions and functioning in children.

Objective: To determine cardiac dimensions and left ventricular (LV) systolic function in children with SCA in steady state and compare with same in healthy haemoglobin type AA controls.

Methodology: Case-controlled, cross-sectional study of 50 subjects aged ≤ 15 years and 50 age- and sex-matched controls to determine and compare aortic root diameter (Ao), left atrium diameters (LAD), LV dimensions and indices of LV function [fractional shortening (FS) and ejection fraction (EF)] using 2-D guided M-mode echocardiography. Body surface areas (BSA) and venous haematocrits were also assessed.

Results: Subjects had significantly higher mean Ao and LAD than controls ($p=0.020$ and $p<0.001$ respectively). The LV dimension indices measured were all significantly higher in subjects, excepting LV-posterior wall diameter in diastole. Almost half (44.0%) of the subjects had LV hypertrophy and almost all (95.5%) were eccentric. Nevertheless, subjects and controls had similar systolic cardiac function [FS (%); 32.04 vs. 32.29, $p=0.871$ and EF (%); 59.94 vs. 60.86, $p=0.326$] and these showed no correlation with age, BSA or haematocrit in both study groups.

Conclusion: Nigerian children with SCA have deviations in cardiac dimensions with enlargements in various echocardiographic indices ranging from 1.1 to 1.4 times those of normal children. Yet, these children retain relatively normal systolic cardiac function.

Keywords: ECHO; Hb SS; Heart

Introduction

Sickle cell anaemia (SCA), a disease of public health significance affects millions of people globally and remains the most common, severe inherited disease in Africa [1]. It is associated with multiple structural and organ dysfunctions including potentially life-threatening cardiovascular complications [2]. Till date, there is no consensus on the cardiovascular function of persons with SCA as the medical literature abounds with conflicting reports. Majority of studies available are ironically from the western world, Asia and the Mediterranean where the clinical presentation and disease severity are less dire in comparison with Africa [3]. Cardiac enlargement has been observed in SCA [4-7] but correlation has not been found with the haemoglobin level [8,9]. Some echocardiography (ECHO) studies report normal left ventricular (LV) function in spite of increase in cardiac size and mass noted [6,9] while others report LV dysfunction in children with SCA [8,10].

Published literature on the cardiac effects of SCA is limited in Africa and Nigeria in particular and again, many of these are works on adults [11]. In Nigeria, there are few ECHO reports [9,12] on children yet, it is here that the disease burden is highest. This informed this present study which aimed at evaluating by ECHO, the impact of SCA on cardiac dimensions as well as LV systolic function in children and analysing these with haemoglobin levels and body surface area (BSA).

Methodology

This was an observational, descriptive, cross-sectional, case-controlled study conducted over six months from February 2011 at the OAUTHC, the main tertiary health facility that serves the Ile-Ife Township of Southwest Nigeria which has a population of 355,341 at the 2006 population census [13]. Subjects were consecutive children with SCA in steady state (i.e. free of infection, pain, or other disease processes) [3] recruited at the paediatric sickle cell outpatient clinic. Exclusion criteria included presence of sickle cell crises, congenital or acquired heart diseases, acute infections, chronic renal failure, hypertension, protein energy malnutrition and/ or blood transfusion within three months of recruitment.

Controls were children who had fully recovered from minor illnesses unrelated to the cardiovascular, respiratory and renal systems

recruited from the general paediatric outpatient unit age- and sex-matched on a ratio of 1:1 with the subjects. They had no inter-current illness, haemoglobin type AA and venous haematocrit of at least 30 percent. The age limits were set at 15 years as the older children are managed in the adult haematology clinic and one year to ensure cooperation of the subjects during ECHO.

Institutional ethical clearance was obtained from the Ethics and Research Committee of the hospital. Parental informed written consents were obtained. Data included age, sex, axillary temperature (°C), respiratory and right radial arterial pulse rates, weight (kg) by SECA® scale, height (cm) measured with a fixed stadiometer, Spirit Height® and the BSA derived using the Mosteller formula [14]: BSA=√{[height (cm) × weight (kg)] ÷ 3600}. Blood pressures (BP) were measured supine using the Accuson® mercurial sphygmomanometer. The average of two readings was documented in mmHg. The systolic BP corresponded to the first Korotkoff sound while the diastolic BP corresponded to the fourth Korotkoff sound [15]. Haematocrits were determined from venous samples spun for five minutes at 10,000 revolutions per second [16].

ECHO measurements were determined by two of the investigators (BO and OS) at the Bethesda Heart Centre (BHC) Ibadan, a non-governmental organization owned by the Save-a-Child's Heart Foundation, Nigeria. The fixed Agilent Sonos (Hewlett Packard)® 4500 ECHO machine equipped with paediatric transducers (3-8 MHz) was used. It has high definition colour-coded Doppler (pulsed and continuous wave) and inbuilt electrocardiographic (ECG) device.

Each child had a precautionary 20 minutes period of rest before thorough repeat physical examinations were conducted with emphasis placed on the cardiovascular and respiratory systems and vital indices (temperature, pulse and respiratory rates, and BP).

Each child had trans-thoracic studies in the supine and left lateral decubitus positions [17]. Initial baseline 2-Dimensional (2-D) and colour flow Doppler ECHO were done to exclude structural anomalies of the heart and valves. From the left parasternal long axis, the M-mode recording was derived with the guidance of a simultaneous recording of a 2-D image obtained in order to ensure precision in location and direction of the M-mode cursor [18]. Simultaneously recorded ECG lead was used as a reference to accurately determine end systole and end diastole. The measurements were made using the American Society of Echocardiography (ASE) guidelines [19] of the leading edge to leading edge methodology. The measurements were calliper aided to ensure uniformity and accuracy and were made to the nearest 0.01 cm.

The Echocardiographic measures assessed were as follows:

- Cardiac dimensions:

  The aortic root diameter (Ao) [20]

  The left atrium diameter (LAD) [20]

  Left ventricular measurements:

  Left ventricle end diastolic diameter (LV-EDD) [20]

  Left ventricle end systolic diameter (LV-ESD) [20]

  Interventricular septal diameter in diastole (IVS-Dd) [20]

  Left ventricle posterior wall thickness in diastole (LV-PWDd) [20]

  The left ventricular mass (LV-M) derived using the Paediatric LV-M calculator [21]

  Left ventricular mass index (LV-MI) [15,22]

  Relative wall thickness (RWT) [23]

- LV systolic function:

  Fractional shortening (FS) [17]

  Ejection fraction (EF) [17]

Data analysis was with SPSS 17.0 for Windows. Means, standard deviations (SD), medians and ranges were generated. Student independent t-test, Pearson chi-squared test of association (χ^2) with Yate's correction applied and Pearson correlation coefficients (r) were used for comparison as necessary. Statistical significance was established when values of probability 'p' were less than 0.05 and 95% confidence intervals of difference (CI) excluded unity.

Results

One hundred children (50 subjects with SCA and 50 Haemoglobin type AA controls) were recruited. Their ages ranged between 2 and 15 years [median=6.0 years]. In each group, 23 (46.0%) were boys (male:female ratio=1:1.17). Mean values of their anthropometry, vital clinical indices and haematocrit are shown and compared in Table 1. Subjects were significantly shorter, lighter in weight and had smaller BSA than controls. Their blood pressures and haematocrits were also, significantly lower.

S.No.	Variables	Subjects (n=50) Mean (SD)	Controls (n=50) Mean (SD)	t	p
1.	**Weight (kg)**	20.73 (7.89)	26.97 (11.09)	3.24	0.002
2.	**Height (cm)**	118.31 (19.20)	127.87 (19.77)	2.45	0.016
3.	**BSA (m^2)**	0.82 (0.22)	0.97 (0.27)	3.05	0.003
4.	**Temperature (°C)**	36.70 (0.34)	36.64 (0.26)	0.99	0.324
5.	**Respiratory rates (Cycles/min)**	26.73 (4.40)	24.42 (3.91)	2.77	0.007
6.	**Pulse rates (Beats/min)**	95.54 (19.42)	91.96 (14.30)	1.05	0.296
7.	**Systolic BP (mmHg)**	95.22 (9.34)	99.50 (11.34)	2.06	0.042
8.	**Diastolic BP (mmHg)**	53.52 (6.69)	61.28 (8.58)	5.04	<0.001
9.	**Haematocrit (%)**	24.38 (3.61)	36.40 (2.85)	18.48	<0.001

Table 1: Clinical parameters of the subjects and controls.

Details of the various ECHO dimensions and LV systolic functional parameters studied are shown in Table 2. Subjects had significantly higher mean aortic root and left atrium diameters than controls. Also, the mean LAD:Ao ratio computed for children in both groups was significantly higher in the subjects.

The mean values of each of the indices of LV dimensions measured were all higher in the children with SCA than the controls (Table 2). These observations were all statistically significant excepting the differences in the means of the LV-PWDd for which the subjects had higher values but the observed difference which below levels set to conclude statistical significance. Twenty-two (44.0%) of the subjects

had LV-MI greater than 51 g/m$^{2.7}$ [which is cut-off point indicative of left ventricular hypertrophy (LVH)] as against only four (8.0%) of the controls. This higher proportion of children with LVH among the SCA subjects compared with controls was significant statistically (Yates' corrected χ^2=15.02, df=1 and p=0.000106).

S.No.	Variables	Subjects n=50 Mean (SD) [Range]	Controls n=50 Mean (SD) [Range]	t	95% CI	p
1.	**Ao (cm)**	2.07 (0.32)	1.93 (0.27)	2.36	0.02-0.26	0.02
		[1.44-2.78]	[1.43-2.59]			
2.	**LAD (cm)**	3.29 (0.40)	2.74 (0.39)	6.96	0.39-0.71	0.001
		[2.27-4.33]	[1.98-3.76]			
3.	**LAD/Ao ratio**	1.59 (0.19)	1.44 (0.18)	4.05	0.08-0.22	<0.001
		[1.14-1.97]	[1.13-1.80]			
4.	**LV-EDD (cm)**	4.33 (0.53)	3.83 (0.41)	5.28	0.31-0.69	<0.001
		[3.14-5.56]	[3.11-5.02]			
5.	**LV-ESD (cm)**	2.95 (0.42)	2.61 (0.42)	4.05	0.17-0.51	<0.001
		[1.65-3.96]	[1.94-3.60]			
6.	**IVS-Dd (cm)**	0.63 (0.17)	0.54 (0.12)	3.06	0.03-0.15	0.003
		[0.28-1.04]	[0.25-0.89]			
7.	**LV-PWDd (cm)**	0.66 (0.15)	0.63 (0.13)	1.07	-0.03-0.09	0.288
		[0.32-0.94]	[0.42 –0.95]			
8.	**LV-M (g)**	84.73 (33.60)	60.63 (22.35)	4.22	12.77-35.43	<0.001
		[30.64-187.90]	[28.20-122.30]			
9.	**LV-MI (g/m$^{2.7}$)**	53.55 (18.44)	32.59 (10.77)	6.94	14.97-26.96	<0.001
		[14.04-115.76]	[15.62-60.68]			
10.	**FS (%)**	32.04 (6.44)	32.29 (5.66)	0.21	-2.16-2.66	0.837
		[15.00-47.30]	[23.40-46.20]			
11.	**EF (%)**	59.94 (9.19)	60.86 (7.96)	0.54	-2.49-4.33	0.594
		[32.10-80.00]	[47.50– 78.50]			

Table 2: Echocardiographic dimensions of the subjects and controls.

To determine the types of LVH, the 26 children with ECHO evidence suggestive of LVH had their 'relative wall thickness' (RWT) calculated. Twenty-one (95.5%) of the 22 subjects with SCA and LVH had a RWT>0.41 (which is normal) and indicative of eccentric LVH. The only child among the SCA subjects with LVH had RWT of 0.45 thus, making this LVH concentric in nature. The four controls with abnormal LV-MI all had eccentric LVH with normal RWT of less than 0.41.

The indices of LV function (FS and EF) were both slightly lower in the SCA subjects than obtained for controls (Table 2) but these differences were not significant statistically (FS; p=0.835 and EF; p=0.595).

The correlations between the ECHO parameters measured and age, BSA and haematocrits among the subjects and controls are shown in Tables 3, 4 and 5 respectively. All the ECHO dimensions showed significant positive correlation with age in both study groups excepting the LV-MI that correlated negatively with age and this was seen in both groups of children. There was no significant association between age and both systolic functional parameters (FS and EF) in both study groups.

A significant inverse relationship was noted when the LV-MI was correlated with the BSA in both groups of children. All the other ECHO parameters showed positive correlation with the BSA of both subjects and controls. There was however, no significant relationship between the BSA and both indices of LV systolic function of both groups of children.

There was no significant relationship demonstrated between any of the studied ECHO parameters and the haematocrit level in both the subject and control groups.

S.No.	Parameters	SCA Subjects n=50		Hb AA Controls n=50	
		r	p	r	P
1.	Ao (cm)	0.78	<0.001	0.79	<0.001
2.	LAD (cm)	0.62	<0.001	0.73	<0.001
3.	LAD/Ao ratio	-0.34	0.017	0.06	0.694
4.	LV-EDD (cm)	0.7	<0.001	0.66	<0.001
5.	LV-ESD (cm)	0.62	<0.001	0.61	<0.001
6.	IVS-Dd (cm)	0.51	<0.001	0.43	0.002
7.	LV-PWDd (cm)	0.62	<0.001	0.48	<0.001
8.	LV-M (g)	0.72	<0.001	0.72	<0.001
9.	LV-MI (g/$m^{2.7}$)	-0.36	0.011	-0.38	0.006
10.	FS (%)	-0.1	0.486	-0.27	0.057
11.	EF (%)	-0.12	0.406	-0.19	0.182

Table 3: Correlation of echocardiographic dimensions with age.

S.No.	Parameters	SCA Subjects n=50		Hb AA Controls n=50	
		R	p	r	P
1.	Ao (cm)	0.753	<0.001	0.796	<0.001
2.	LAD (cm)	0.585	<0.001	0.709	<0.001
3.	LAD/ Ao ratio	-0.317	0.025	-0.025	0.863
4.	LV-EDD (cm)	0.641	<0.001	0.756	<0.001
5.	LV-ESD (cm)	0.67	<0.001	0.644	< 0.001
6.	IVS-Dd (cm)	0.54	<0.001	0.415	0.003
7.	LV-PWDd (cm)	0.594	<0.001	0.615	<0.001
8.	LV-M (g)	0.726	<0.001	0.79	<0.001
9.	LV-MI (g/ $m^{2.7}$)	-0.398	0.004	-0.292	0.04
10.	FS (%)	-0.195	0.175	-0.262	0.066
11.	EF (%)	-0.22	0.125	-0.188	0.19

Table 4: Correlation of echocardiographic dimensions with body surface area.

S.No.	Parameters	SCA Subjects n=50		Hb AA Controls n=50	
		R	P	r	p
1.	Ao (cm)	-0.163	0.259	-0.004	0.977
2.	LAD (cm)	-0.124	0.39	-0.029	0.842
3.	LAD/ Ao ratio	0.045	0.758	0.083	0.568
4.	LV-EDD (cm)	-0.156	0.28	-0.026	0.857
5.	LV-ESD (cm)	0.017	0.907	0.051	0.723
6.	IVS-Dd (cm)	-0.027	0.85	0.233	0.104
7.	LV-PWDd (cm)	-0.183	0.203	0.063	0.666
8.	LV-M (g)	-0.155	0.284	0.112	0.438
9.	LV-MI (g/ $m^{2.7}$)	-0.259	0.07	-0.021	0.886
10.	FS (%)	-0.244	0.087	-0.107	0.458
11.	EF (%)	-0.254	0.075	-0.123	0.395

Table 5: Correlation of echocardiographic dimensions with haematocrit.

Discussion

The impact of SCA on LV dimensions and function in both children and adults has been better studied in the developed world than countries like Nigeria where persons with SCA abound. Our study documents cardiac size and LV systolic function of Nigerian children with homozygous SCA and in addition, correlated these with the age, BSA and haematocrit levels. We found that Nigerian children with SCA have deviations in cardiac dimensions from normal children with enlargements noticed on ECHO ranging from 1.1 to 1.2 times in the Ao and LAD. Similar dilatations of the LA and Ao had been earlier documented in children [9,24,25] as well as adults with SCA [26,27].

Also, we observed increases in the entire LV dimensions of about 1.1 to 1.4 times those of normal children. These were all significantly higher in children with SCA, excepting the LV-posterior wall diameter in diastole just as previously documented [5,9]. However, some other authors have documented increase in this parameter in children with SCA [12,28]. Lester et al. [4] observed increased wall thickness in only 20 percent of the older children with SCA. Clinicopathologic studies by Gerry et al. [29] have shown greater hypertrophy of the left and right ventricles in adults than in children. This appears reasonable considering the progressive increase in LV wall stress in such patients over many years. The younger age population of the present study may be responsible for the lack of significant increase noted in the LV free wall thickness. Even the interventricular septal diameter in diastole (IVS-Dd) of SCA subjects was significantly larger than that of controls (p=0.007). This is contrary to findings of Lamers et al. [10] who did not find any difference in septal thickness in the paediatric sickle cell patients even though size and age of the population he studied were similar to ours. However, Cipollotti et al. [6] reported findings similar to ours in a study of 38 Brazilian children and adolescents.

We also observed that left ventricular hypertrophy (LVH) is a prominent ECHO feature of children with SCA as seen in almost half (44.0 percent). The left ventricular mass (LV-M), which is an estimate of the weight of the LV, was found to be significantly increased in the subjects in our study. The LV-M is derived from the LV-EDD, IVS-Dd and LV-PWDd, and because these parameters were increased in the SCA group, it was only inevitable that the LVM of these patients would be increased. LV-M is thought to increase in SCA when the chamber dilatation alone cannot compensate for the increasing

demands placed on the myocardium [26]. Heart size is closely associated with body size [27]. Left ventricular mass index (LV-MI) is calculated to standardize measurements of LVM [15]. Several methods for indexing left ventricular mass have been reported, but it is recommended that height raised to the power of 2.7 ($m^{2.7}$) be used as described by deSimone et al. [22]. This method accounts for close to the equivalent of the effect of lean body mass and excludes the effect of obesity and blood pressure elevation on LV-M [15]. For children and adolescents, a conservative cut point that determines the presence of LVH is 51 $g/m^{2.7}$. All but one of our SCA subjects with LVH had normal relative wall thickness values of less than 0.41 [23], showing eccentric LVH. Eccentric hypertrophy is associated with intermediate risk for cardiovascular outcomes while the concentric pattern is associated with higher risk [15]. Johnson et al. [30] had earlier reported similar findings. The LV-M increases in SCA when chamber dilatation alone can no longer compensate for the increasing demands placed on the myocardium [26]. Apart from the volume overload which occurs in SCA, sickling of the blood cells occurring in the microvasculature may create additional strain on the heart thus probably inducing ventricular hypertrophy [26].

Thus, it appears agreed upon in the literature that SCA leads to a chamber enlargement of the LA and LV. Since, ascertainment of the LV-MI is very helpful in clinical decision-making; the presence of LVH can be an indication for initiating or intensifying pharmacologic therapy [15].

Cardiac enlargement has been long recognized as part of the clinical manifestation of SCA [31]. Several other authors have documented similar findings in children with SCA [4,6,9,10]. In SCA, there is a double burden imposed on the cardiovascular system, namely the haemodynamic effect of the anaemia and the influence of the myocardial insult caused by the sickling process [32]. To compensate for the chronically reduced oxygen carrying capacity, cardiac output is increased in persons with SCA [32,33]. Cardiac output is dependent on heart rate and stroke volume [6]. In chronic anaemia, the heart rate is increased due to hypoxia-stimulated chemoreceptors and increased sympathetic activity [34]. However, the successful adaptation to chronic SCA results in only minimal increases in heart rate [28]. Thus, the major contributor to the increased cardiac output in these children is an increase in stroke volume [25,33]. The preload increases owing to the volume overload and afterload is reduced because of decreased peripheral resistance [6]. Thus, it is not surprising to find significant dilatation of the cardiac chambers we report.

In the present study, cardiac function was assessed using the fractional shortening (FS) and the ejection fraction (EF). Results showed that there was no difference in these functional parameters for both the subjects and controls. This suggests normal LV contractility in children with SCA despite the increased dimensions of the LV. Lester [4] found that resting parameters of ventricular function based on FS, EF and the mean velocity of circumferential fibre shortening (which we were limited in studying) were comparable to that of the controls.

The functional parameters (EF and FS) did not show any correlation with age. This has also been reported by other workers [4,9,12]. From this findings it can be deduced that percentage of blood ejected from the heart and the degree of cardiac contractility remains the same in spite of a marked increase in LV size during normal growth and development.

There was a significant relationship between the direct ECHO parameters and the BSA. Other workers have reported similar findings [4,12]. The functional parameters however were independent of the BSA. This implies that the percentage of blood ejected and the degree of cardiac contractility with each heart beat remains the same irrespective of the BSA.

With respect to the haematocrit level, the value obtained in the SCA subjects was significantly lower than that obtained in the healthy AA controls. This was not unexpected because of the chronic anaemia associated with SCA. However, we found no correlation between the haematocrit levels, and the ECHO parameters and measures of left ventricular systolic function in both the SCA and the control groups. This is similar to the findings of Omokhodion et al. [9] and Animasaun et al. [13] that carried out similar studies in western Nigeria as well as Cipollotti et al. [6] and Chung et al. [35]. However, Taksande et al. [5] reported significant increase in LV dimensions and mass proportional to the degree of anaemia. Also, Covitz et al. [25] reported that the degree of dilatation was significantly associated with the severity of anaemia.

The human heart is indeed a three-dimensional structure thus; where the resources are available for 3-D echocardiography volumetric indices such as LA volume and LA volume index, (LAVi) as well as LV volumetric analyses should be undertaken. Our study was limited in this regards as well as the fact that we embarked on this study from a single centre.

It has been suggested that the heart is affected as part of the disease process in patients with SCA as a result of the chronic LV volume overload and sustained high cardiac output caused by the severe long standing anaemia [4]. However, this study and previous investigations have consistently failed to show impairment in systolic performance in children with SCA. Thus, diastolic dysfunction remains the alternative explanation for the cardiac symptoms in SCA [13]. Thus, early and routine echocardiography in children with sickle cell anaemia would be of great benefit in the identification of structural abnormalities and this may enhance early interventions which may prevent such systolic dysfunctions that have being noted in adults with SCA.

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