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Comparison of Diastolic Function of Homozygous Sickle Cell Anaemia with Haemoglobin AA Children Using Basic Mitral Inflow Doppler Echocardiography

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Authors' contributions

This work was carried out in collaboration between all authors. Authors BTO and OJA designed the study. Authors BTO, OS and AO did the data collection and interpretation. Authors BTO and OJA wrote the first draft of the manuscript. Authors BTO, OS and AO managed the literature searches, analyses of the results. All authors read and approved the final manuscript.

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ABSTRACT

Aims: Sickle cell anaemia (SCA) remains the most prevalent and arduous inherited disease in Nigeria. Various adverse cardiovascular consequences have been documented including cardiac chamber enlargement and left ventricular (LV) hypertrophy. Diastolic dysfunction, a recognized risk factor for death, has been reported in adults however the time of onset remains unknown. A dearth of literature persists about the impact of SCA on diastolic function among children. This study aimed to determine LV diastolic function in children with SCA in steady state and compare with apparently healthy haemoglobin type AA controls.
Study Design: Observational, case-controlled, cross-sectional study.

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Place and Duration of Study: Department of Paediatrics, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife and the Bethesda Heart Centre, Ibadan, Nigeria, six months.
Methodology: Fifty subjects aged ≤ 15 years and 50 age- and sex-matched controls to determine and compare basic mitral inflow indices of diastolic function using 2-D guided Doppler echocardiography.
Results: Subjects had significantly higher left atrial and LV dimensions, mean E-wave velocity (1.08 versus 0.94 m/ s, p = .001) and A-wave velocity (0.58 versus 0.52 m/ s, p < .001) than controls. Slightly higher E/ A ratio and longer deceleration time were observed in subjects but without statistical significance [p = .48 and p = .33 respectively]. E- and the A-wave velocities in subjects did not correlate with age or BSA unlike in controls which showed negative correlations. There was however significant negative correlation between haematocrit and the A-wave velocity and the E/ A ratio of subjects.
Conclusion: Even in steady state, children with SCA have relatively abnormal early and also late LV diastolic filling. These did not correlate with age or BSA. Haematocrit showed significant correlation with late diastolic LV filling. Evaluation of left ventricular diastolic function should be routinely used in cardiac assessment of children with SCA.

Keywords: Cardiac function; diastolic dysfunction; echocardiography; Hb SS; heart.

1. INTRODUCTION

Sickle cell anaemia (SCA) is widespread in Africa and with globalization, has become the most common, severe inherited genetic disease worldwide [1,2]. It is associated with multiple organ dysfunction including potentially life threatening cardiac complication [2,3]. Abnormalities in cardiac function has been documented in patients with SCA [3-5]. Premature and sudden unexpected death have also been described [4-7] but the exact mechanism is not well understood. Reports of studies point attention to emerging cardiac pathologies in sickle cell disease [4,8]. The exact time when these cardiac abnormalities set in is not known. Several studies in both children and adults have shown that cardiac size and dimensions are increased in children with SCA, in spite of this left ventricular systolic function remains preserved [9-11].

Diastolic dysfunction precedes abnormalities in systolic function [12]. It is now widely understood that almost all forms of acquired heart disease are associated with a component of left ventricular diastolic dysfunction [13]. There is evidence that diastolic dysfunction and pulmonary hypertension (PH) portend poor prognoses in patients with SCD [14]. Studies documenting diastolic function in children with SCA in Africa are sparse. Hence, this study which aimed to characterize diastolic function in children with SCA (Hb SS) aged one to fifteen years in steady state, and to correlate these parameters with their age, body surface area and haematocrit levels and compare these with those of healthy age- and sex-matched controls with haemoglobin genotype AA.

2. MATERIALS AND METHODS

2.1 Study Setting

This was an observational, descriptive, cross-sectional, case-controlled study conducted over a six-month period at the Department of Paediatrics, Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile-Ife and the Bethesda Heart Centre, Ibadan, Nigeria. The OAUTHC is the main tertiary health facility that serves the Ile-Ife township of Southwest Nigeria [15].

2.2 Study Design and Data Collection

Subjects were 50 consecutive children with SCA (Hb SS) in steady state (i.e. free of infection, pain, or other disease processes) [16] recruited at the paediatric sickle cell outpatient clinic. As at the time of the study none of the subjects had been chronically transfused. 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 echocardiography sessions.

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 [17]: BSA=√{[height (cm) × weight (kg)] ÷ 3600.

Echocardiography measurements were determined by two of the investigators (BO and OS) at the Bethesda Heart Centre (BHC) Ibadan, a non-governmental organization operated 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 [11]. Initial baseline 2-Dimensional (2-D) and colour flow Doppler ECHO were done to exclude structural anomalies of the heart and valves. Dimensions of the left cardiac chamber were taken and recorded for each child. From the apical four chamber view, a two-dimensionally directed pulsed sample volume was place at the tips of the mitral valve leaflets in all the children using the American Society of Echocardiography (ASE) guidelines. We evaluated left ventricular diastolic function by assessing early and late mitral inflow velocities (E- and A-wave respectively), E/ A ratio and deceleration time for the subjects and the controls.

2.3 Ethical Approval

Institutional Ethical clearance was obtained from the Ethics and Research Committee of the OAUTHC, prior to commencement of the study. Parental informed written consents and assent from the study participants were obtained.

2.4 Statistical Analysis

Data was processed with SPSS 17.0 for windows statistical software (SPSS Inc., Chicago, IL, USA) using descriptive and inferential statistics. Means, standard deviations (SD), medians and ranges were generated. The associations between mitral inflow indices of diastolic function and age, venous haematocrit and body surface area were determined using linear logistic regression.

Student independent t-test, Pearson chi-squared test of association ($\chi 2$) 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 .05.

3. RESULTS AND DISCUSSION

One hundred children (fifty subjects with SCA and fifty haemoglobin type AA controls) were recruited. Their ages ranged between 2 and 15 years. The median age was 6.0 years in both groups. There were 23 (46.0%) males and 27 (54.0%) females in each group, giving a male to female ratio of 1: 1.17.

The mean values of their weights, heights, body surface areas and venous haematocrits are provided and compared in Table 1. The subjects with SCA were significantly shorter, lighter in weight and had smaller BSA than haemoglobin type AA controls. Their venous haematocrits were also significantly lower. Also from the same table, it can be seen that their pulse rates, systolic and diastolic blood pressures and venous haematocrits were also significantly lower.

The details of the mean aortic root and left atrial diameters of the subjects and controls are shown in Table 2. The mean aortic root diameter (AO) and the left atrial diameter (LAD) in the SCA subjects were higher than in the controls. The differences were statistically significant ($p = .02$, $p < .001$ respectively). The ratio of the LAD: AO was computed for both the subject and the control groups and the mean (SD) of these values was significantly higher in the subjects ($p < .001$).

Left ventricular measurements are shown in Table 3. There were four (4) measured LV indices and two (2) computed indices. The mean left ventricular end diastolic diameter (LVEDD) and the mean left ventricular end systolic diameter were both higher in the subjects than in the control group. These differences were statistically significant ($p < .001$). Similarly, the mean interventricular septal diameter in diastole (IVSDd) was higher in the subjects than in the

control group and this difference was statistically significant (p = .007). The mean left ventricular posterior wall diameter in diastole (LVPWDd) was higher in the subjects than in the controls however, the difference was not statistically significant (p = .391).

The left ventricular mass was derived for both groups. The mean LVM of the SCA subjects [84.73 (33.60) g] was higher than the LVM obtained for the controls [60.63 (22.35) g]. This difference was statistically significant (p < .001).

The left ventricular mass index (LVMI) was also derived for both groups using the formula: LVM ÷ Height $(m)^{2.7}$. The mean (SD) LVMI of the SCA subjects [53.55 (18.44) g/ $m^{2.7}$] was much more than the LVMI obtained for the controls [32.59 (10.77) g/ $m^{2.7}$]. This difference was statistically significant (p < .001).

Twenty-two (44.0%) of the subjects had LVMI greater than 51g/ $m^{2.7}$ [which is indicative of left ventricular hypertrophy (LVH)] as against four (8.0%) of the controls (Yates' corrected $\chi 2$ = 15.02, df = 1 and p < .001). The higher proportion of children with LVH among the SCA subjects compared with those in the Hb AA control group was statistically significant.

For these 26 children with echocardiographic evidence suggestive of LVH, the 'Relative Wall Thickness' (RWT) was calculated with the formula: RWT = [IVSDd + LVPWDd] ÷ LVEDD; Twenty-one of the children with SCA had a RWT less than 0.41 (which is normal) and this confirms that the left ventricular hypertrophy identified by echocardiography in these children is of the eccentric type. Only one of the SCA subjects had a concentric form of left ventricular hypertrophy (with a RWT of 0.45). The four children in the control group with LVH all had the eccentric type (RWT less than 0.41).

The details of the echocardiographic parameters of diastolic function are shown in Table 4. With respect to the values of the E-wave and the A-wave velocities obtained in the subjects were significantly higher than those of the control group [E-wave; 1.08 m/ s (0.18) versus 0.94 m/ s (0.12) and p < .001 with A-wave; 0.58 m/ s (0.13) vs. 0.51 m/ s (0.07) and p = .001]. However, when the E/ A ratio of both groups were compared there was no statistically significant difference (p = .46). The deceleration time for the subjects was longer than that of control group. However, this difference was not found to be statistically significant (p = .33).

Table 1. Clinical parameters of the subjects and controls

Variables	Subjects n = 50 Mean (SD)	Controls n = 50 Mean (SD)	t	p
1. Height (cm)	118.31 (19.20)	127.87 (19.77)	2.45	.016
2. Weight (kg)	20.73 (7.89)	26.97 (11.09)	3.24	.002
3. Body surface area (m^2)	0.82 (0.22)	0.97(0.27)	2.96	.004
4. Temperature (^oC)	36.70 (0.34)	36.64 (0.26)	-1.02	.311
5. Respiratory rate (cycles/ minute)	26.73 (4.40)	24.42 (3.91)	-1.58	.117
6. Pulse rate (beats/ minute)	95.54 (19.42)	91.96 (14.3)	-1.05	.297
7. Systolic blood pressure (mmHg)	95.22 (9.34)	99.50 (11.34)	2.06	.042
8. Diastolic blood pressure (mmHg)	53.52 (6.69)	61.28 (8.58)	5.04	< .001
9. Haematocrit (%)	24.38 (3.61)	36.40 (2.85)	18.47	< .001

Table 2. Aortic root and left atrial diameters of the subjects and controls

Variables	Subjects n = 50 Mean (SD) [Range]	Controls n = 50 Mean (SD) [Range]	t	p
1. AO (cm)	2.07 (0.32) [1.44 - 2.78]	1.93 (0.27) [1.43 - 2.59]	- 2.36	.02
2. LAD (cm)	3.29 (0.40) [2.27 - 4.33]	2.74 (0.39) [1.98 - 3.76]	- 6.96	< .001
3. LAD: AO	1.59 (0.19) [1.14 - 1.97]	1.44 (0.18) [1.13 - 1.80]	- 4.10	< .001

Table 3. Left ventricular echocardiographic measurements of the subjects and controls

Variables	Subjects n = 50 Mean (SD) [Range]	Controls n = 50 Mean (SD) [Range]	t	p
1. Left ventricular end diastolic diameter (cm)	4.33 (053) [3.14 - 5.56]	3.83 (0.41) [3.11 - 5.02]	- 5.30	< .001
2. Left ventricular end systolic diameter (cm)	2.95 (0.42) [1.65 - 3.96]	2.61 (0.42) [1.94 - 3.60]	- 4.01	< .001
3. Interventricular septal diameter in diastole (cm)	0.63 (0.17) [0.28 – 1.04]	0.54 (0.12) [0.25 – 0.89]	- 2.76	.007
4. Left ventricular posterior wall diameter in diastole (cm)	0.66 (0.15) [0.32 - 0.94]	0.63 (0.13) [0.42 - 0.95]	- 0.86	.39
5. Left ventricular mass (g)	84.73 (33.60) [30.64 - 187.90]	60.63 (22.35) [28.20 - 122.30]	- 4.22	< .001
6. Left ventricular mass index (g/ $m^{2.7}$)	53.55 (18.44) [14.04 - 115.76]	32.59 (10.77) [15.62 - 60.68]	- 6.94	< .001

Table 4. Left ventricular functional parameters of the subjects and controls

Variables			Subjects n = 50 Mean (SD) [Range]	Controls n = 50 Mean (SD) [Range]	t	p
A.	Systolic function	1. Fractional shortening (%)	32.04 (6.44) [15.00 – 47.30]	32.29 (5.66) [23.40 – 46.20]	0.21	.84
		2. Ejection fraction (%)	59.94 (9.19) [32.10 – 80.00]	60.86 (7.96) [47.50 – 78.50]	0.53	.60
A.	Diastolic function	1. E wave (m/ s)	1.08 (0.18) [0.73 – 1.53]	0.94 (0.12) [0.71 – 1.18]	- 4.46	< .001
		2. A wave (m/ s)	0.58 (0.13) [0.36 – 0.89]	0.51 (0.07) [0.33 – 0.70]	- 3.31	.001
		3. E/ A Ratio	1.90 (0.32) [1.35 – 2.78]	1.86 (0.24) [1.41 – 2.70]	- 0.73	.46
		4. Deceleration time (ms)	86.90 (20.41) [50.00 – 150.00]	83.40 (15.27) [50.00 – 120.00]	- 0.96	.33

Correlation of diastolic parameters with age, BSA and haematocrit of the subjects and controls are detailed in Table 5. There was no significant correlation between any of the diastolic parameters with age in both subject and control groups except the E- and A-wave velocity of the subjects that showed a significant negative correlation with age [p = .002, p = .01 respectively]. When the diastolic parameters were correlated with the body surface area. Only the E- and A-wave velocities in the control group showed a significant negative correlation with the body surface area [p = .003, p = .026].

With the exception of the A-wave velocity and the E/ A ratio of the SCA subjects, which both demonstrated a significant negative relationship (p = .015, p = .029) when correlated with the haematocrit level in the subjects there was no relationship between the other echocardiographic parameters and haematocrit in both the subject and control groups.

Sickle cell anaemia results in dilation of the cardiac chambers, left ventricular hypertrophy (LVH) and an increase in left ventricular mass (LVM). In spite of these, LV systolic function remains unimpaired. We reported these findings in an earlier study [11]. Increase in LVM results from the compensatory hypertrophy that occurs in response to ventricular dilation. As a consequence of the LVH, patients with SCA tend to have increased LV stiffness which progresses to diastolic dysfunction and congestive heart failure (CHF), which are manifested mostly in adulthood [18]. These complications are associated with early mortality [18].

Table 5. Correlation of diastolic parameters with age, BSA and haematocrit of the subjects and controls

Parameters	Subjects		Controls	
	r	*p*	*r*	*p*
Correlation of diastolic parameters with age				
1. E wave (m/ s)	- 0.202	.16	- 0.423	.002*
2. A wave (m/ s)	- 0.123	.39	- 0.361	.01*
3. E/ A Ratio	- 0.007	.96	- 0.009	.95
4. Deceleration time (ms)	0.203	.19	0.156	.28
Correlation of diastolic parameters with BSA				
1. E wave (m/ s)	- 0.258	.07	- 0.410	.003*
2. A wave (m/ s)	- 0.183	.20	- 0.315	.026*
3. E/ A Ratio	- 0.014	.92	- 0.058	.922
4. Deceleration time (ms)	0.238	.097	0.200	.163
Correlation of diastolic parameters with haematocrit				
1. E wave (m/ s)	- 0.159	.27	- 0.036	.80
2. A wave (m/ s)	- 0.342	.015*	0.105	.46
3. E/ A Ratio	- 0.309	.029*	- 0.256	.07
4. Deceleration time (ms)	0.007	.96	0.151	.29

r: Pearson's Correlation Coefficient.
**: Statistically significant*

In this study, we assessed diastolic function in children with SCA by determining the mitral inflow velocities, using Doppler echocardiography [19]. The amplitude of the E- and A-waves and the deceleration time were measured. The amplitude of the mitral inflow E- and A-waves obtained in the subjects were significantly higher than that of the control group however there was no statistically significant difference in the E/ A ratio for both groups. The E/ A ratio is a traditional index of left ventricular filling [19]. The deceleration time in the subjects was shortened but not significantly so, when compared with the value obtained for the control group. From this study, it is therefore clear that the patients with SCA had measurable abnormalities in the diastolic filling of the left ventricle. However, it is difficult to fit these patients into a specific cardiomyopathic pattern due to diastolic dysfunction. These changes, when considered together with increased left ventricular dimensions and muscle mass could possibly indicate early diastolic dysfunction. Diastolic dysfunction has been identified in adult patients with sickle cell anaemia however, the time of onset of this dysfunction remains largely unknown.

AboHadeed et al. [20], studied diastolic function in 85 children with SCA, they reported that there was no statistically significant difference in the E-wave and the A-wave velocities [p = .629, p =.629] respectively] obtained for both the subject and control. The E/A ratio was for the subject and control groups were also similar [p = .351]. However, on further investigation with Doppler tissue imaging they reported myocardial dysfunction in this group of children with sickle cell anaemia. This was unlike what we obtained in this present study. The difference in the finding could probably be accounted for by the selection criteria of the patients studied. Although the patients we studied were age and sex- matched, there was a significant difference in the weight and body surface area of the subjects and controls. AboHadeed et al. [20] reported no significant difference between the studied groups regarding age, gender, body weight, body surface area. Of the 85 children with SCA they studied, 38 received chronic transfusions (2 to 3 times/ year) and were on iron chelation therapy. None of our subjects had had chronic transfusion therapy at the time of the study, although more than three quarters of them had received blood transfusion(s) in the past.

Taksande et al. [9] similarly reported increased amplitudes of the E- and A- waves in the SCA group, however this increase was not found to be of statistical significance. In a large study involving 73 SCA children, Zilberman et al. [21] reported that both the early E and late A mitral inflow velocities were higher in the SCA group than in the controls, so their E/ A ratio remained normal. However, it was only after the addition of tissue Doppler imaging that they were able to

demonstrate diastolic abnormalities in their subjects. Seliem et al. [22] reported increase in the height of the A wave, a decreased E/ A ratio with a shortened deceleration time in the paediatric SCA subjects they studied. They could not identify a specific cardiomyopathic pattern due to diastolic dysfunction.

In a large study of patients with sickle cell anaemia, Caldas et al. [14] reported a significant difference in the E wave and A wave velocities of the SCA subjects and the control group [p = .00 in both instances]. Unlike what we obtained in our study, there was a significant difference in the E/ A ratio and the deceleration time they reported [p = .00, .01 respectively]. The difference in our findings may have been due to the cohort of patients studied. Their patients had a high incidence of vaso-occulsive events and almost half of the group were in New York Heart Association (NYHA) class II-III. None of our patients had dyspnea although the mean respiratory rate was higher in our subjects, though this difference was without statistical significance [p= .117].

Chronic anaemia from any cause is associated with several changes in cardiovascular haemodynamics [23,24]. These include left ventricular dilatation and hypertrophy as well as the other cardiac dimension derangements which are compensatory mechanisms for the long-standing volume overload. Diastolic filling abnormalities (both early and late mitral flow) of the left ventricle were observed among the children with SCA in this study yet, this did not fit any distinct pattern of diastolic dysfunction. Left ventricular diastolic dysfunction in sickle cell anaemia is associated with increased morbidity and mortality [25]. There is evidence that diastolic dysfunction in sickle cell anaemia contributes to pulmonary hypertension and represents an independent risk factor for mortality in these patients [26]. Sudden death is a recognized risk. Further cardiac investigations are important in identifying patients at risk and treating them early. This may need a larger sized study that may utilize other sensitive echocardiographic indices such as tissue Doppler imaging [21] to unravel the specific abnormality of diastolic dysfunction.

4. CONCLUSION

It is concluded that diastolic function of the left ventricle in children with SCA relative to the normal children is abnormal to such an extent that their early diastolic filling as well as late diastolic filling is about 1.1 times higher. However, other indices of diastolic function i.e. E/ A ratio and the deceleration time were similar. These indices did not show any significant relationship with the body surface area in the children with SCA unlike the Hb AA controls in which there was an inverse relationship between the E wave and the A wave, and the body surface area. Haematocrit showed significant correlation with late diastolic left ventricular filling in the sickle cell anaemic children.

It is recommended that evaluation of diastolic function of the left ventricle should be routinely used in cardiac assessment of children with sickle cell anaemia in order to identify of diastolic dysfunction and institute appropriate management early enough. This would help to reduce morbidity and mortality in these vulnerable children.

CONSENT

All authors declare that written informed consent was obtained from the parents of the study participants.

ETHICAL APPROVAL

Institutional Ethical clearance was obtained from the Ethics and Research Committee of the OAUTHC, Ile-Ife, Nigeria.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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