



Topic: Echocardiographic Evaluation of Left Ventricular Systolic and Diastolic Function in Nigerians with Sickle Cell Disease

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Abstract

Introduction: Sickle cell disease (SCD) is chronic, inherited haemoglobin disorder, associated with chronic tissue ischemia which may adversely affect any organ system. Chronic anaemia in SCD results in cardiac chamber dilatation with compensatory increase in left ventricular mass and varying degree of diastolic dysfunction that has been a strong independent predictor of mortality in patients with SCD. There is paucity of echocardiographic studies on adults Nigerians with SCD. This study therefore, aimed to assess left ventricular systolic and diastolic function among sickle cell disease patients in Kano State, North-Western Nigeria. **Methods:** The study was cross-sectional and comparative conducted at the SCD clinic and Medical/outpatient (MOP) clinic of Murtala Muhammad Specialist Hospital (MMSH), on eligible patients aged 13 years and above. One hundred patients with SCD (HbSS) were recruited as the study group while 100 non SCD (HbAA) patients, matched for age and sex served as controls. Left and right atrial and ventricular dimensions, left ventricular (LV) wall thickness, LV mass index and LV contractility variables were obtained. Parameters of LV diastolic function were also evaluated. **Results:** There were increases in the left atrial and left ventricular dimensions, left ventricular volumes and left ventricular mass (LVM) of the SCD patients. LV ejection fraction was equivalent, though there was evidence of left ventricular diastolic dysfunction in up to 36%. **Conclusion:** Left ventricular diastolic dysfunction may complicate cases adults with SCD.

Subject Areas

Cardiology

Keywords

Left Ventricular Systolic Function, Left Ventricular Diastolic Function, Sickle Cell Disease, Nigerians

1. Introduction

Sickle cell disease is an important autosomal recessive haemoglobin disorder characterized by recurrent episodes of haemolytic and vaso-occlusive crises due to entrapment of red blood corpuscles in the micro vasculature leading to ischaemia—reperfusion injury and infarction in the multiple organ systems. The poorly controlled lifelong haemolytic anaemia and recurrent episodes of organ infarction ultimately lead to a progressive systemic vasculopathy and chronic organ failure [1].

Cardiac complications are a common feature of SCD and are felt to be an important cause of morbidity and mortality associated with the disease. The chronic anaemia of SCD results in an increase in cardiac output with only minimal increase in heart rate. Left ventricular stroke volume increases with significant LV dilation, and the degree of LV dilation is closely linked to the anaemia [2]. The dilated LV adapts to the increased wall stress by developing eccentric hypertrophy [3]. Eccentric hypertrophy allows the LV to adapt to chronic volume overload by initially preserving diastolic compliance and maintaining normal filling pressures. Overtime, this progressive dilation leads to increased wall stress and an increase in LV mass. Recent studies have shown that diastolic dysfunction is common in children and in adults, and it was found to be an independent risk factor for mortality [4]. Although in the general population diastolic abnormalities are associated with older age, increases in blood pressure, increased LV mass and increased creatinine levels, it is unclear whether these findings in SCD are due to a combination of compensatory hypertrophy secondary to anaemia and LV dilation along with systemic vasculopathy affecting afterload.

Recent large screening echocardiographic studies indicate that LV systolic function is preserved in the majority of SCD patients studied in the resting state, and the presence of segmental wall motion abnormality is rare [4] [5] [6]. LV dysfunction when present is particularly seen in the older patients and those with associated conditions such as hypertension and renal disease.

2. Methods

The study was cross sectional, carried out in Murtala Muhammad Specialist Hospital, a tertiary health institution in Kano State, Nigeria. The study protocol was approved by the Research Ethics Committee of the hospital, before the commencement of the study. It conformed to the Declaration of Helsinki on investigations involving human subjects [7].

2.1. Patient Selection

The study population comprised of patients at least 13 years of age, attending the Sickle cell and General Outpatient (GOP) clinics of the hospital, who consented for the study between 1st June 2016 to 31st December, 2016. There were two subjects groups: Group 1—subjects with confirmed diagnosis of HbSS, (by Hb Electrophoresis) in a clinical stable state, who presented to the Sickle cell clinic for routine follow up and Group 2 (controls)—age and sex, matched subjects with confirmed HbAA (by Hb Electrophoresis) who presented to the GOP with minor ailments. Two hundred patients were recruited and evaluated; 100 in each group. The subjects in each of the groups were consecutively selected, after satisfying the inclusion criteria. Exclusion criteria include subjects < 13 years of age, subjects with hemoglobinopathies other than SCD, had known congenital or acquired cardiac or pulmonary disease. Subjects with inadequate acoustic windows were also excluded.

Using a structured questionnaire, patients' relevant demographic, clinical and laboratory data were obtained. The weight (taken with patients in light clothing) and height (without cap/head gear/shoes) of the patients were measured using a stadiometer. The body mass index (BMI) was then calculated using the formula; $BMI = \text{weight (in Kg)}/\text{height (m}^2\text{)}$. Blood Pressure measurements were performed prior to the echocardiogram [8]. The mean haemoglobin (Hb) levels 1 year preceding the study was calculated.

2.2. Echocardiographic Examination

M-mode and two-dimensional echocardiography, with colour Doppler imaging were performed on all the subjects by two cardiologists, using Toshiba HDI Machine and a 2.5 to 5.0 Hz linear array transducer, according to the recommendation of the American Society of Echocardiography (ASE) [9]. Subjects were examined in the left lateral decubitus position using standard parasternal, short axis and apical views. The M-mode cursor on the 2D scan was moved to specific areas of the heart to obtain measurements according to the recommendations of the committee on M-mode standardization of the ASE [10]. From the M-mode measurements, indices of Left Ventricular (LV) function were derived. Left ventricular systolic function was calculated by Teicholz formula, and LV systolic dysfunction was defined as left ventricular ejection fraction (LVEF) < 50% [11].

Left ventricular diastolic dysfunction was defined and graded using transmitral inflow velocities as: Normal diastolic filling pattern (values of E/A = 1 - 1.5; DT = 160 - 240 ms; IVRT = 70 - 90 ms), Grade I diastolic dysfunction (reduced E/A < 1.0; prolonged DT > 240 ms; and prolonged IVRT > 90 ms), Grade II diastolic dysfunction (E/A 1 - 1.5; DT 160 - 240 and IVRT < 90 ms), Grade III diastolic dysfunction (increased E/A > 1.5; reduced DT < 160 ms and IVRT < 70 ms). (E = early rapid filling wave; A wave = filling wave due to atrial contraction; DT = deceleration time; IVRT = isovolumic relaxation time) [12].

2.3. Statistical Analysis

Data analysis was done using SPSS version 21.0. Quantitative variables were expressed as means and standard deviations. Qualitative variables were expressed as percentages. The chi-square test was used in comparing proportions, while Student's t-test was used to compare means. A p-value of <0.05 was considered significant for all comparisons.

3. Results

The socio-demographic and laboratory characteristics of the 100 SCD subjects and 100 control subjects are shown in **Table 1**. The mean diastolic blood pressure, body weight, height, BMI and haemoglobin levels were significantly lower in SCD subjects than in controls. The mean left ventricular end-diastolic dimension (LVEDD) and left atrial dimensions (LAD) were significantly greater in the SCD group than in the control group, whereas the mean interventricular septal thickness in diastole (IVSTd) and left ventricular ejection fraction (LVEF) were not significantly different. Mean left ventricular posterior wall thickness in diastole (LVPWd) and left ventricular mass (LVM) were however, also greater in subjects with SCD than in controls, as shown in **Table 2**.

Left ventricular diastolic function parameters are also shown in **Table 2**. The peak filling rate of the left ventricle during diastole was similar in the SCD when compared with the control group. E wave DT and E/A ratio of peak velocities were significantly lower in patients with SCD than in the control group ($P = 0.02$). Overall, 28 (28%) of the subjects with SCD had some form of diastolic dysfunction. The pattern of LV diastolic dysfunction in the subjects with SCD and controls is shown in **Figure 1**. Grade 3 LV diastolic dysfunction was the commonest form of diastolic dysfunction present in both groups, although statistically significantly more in the SCD group than the controls (18 (18%) vs. 7 (7%), $P \leq 0.001$).

Table 1. Demographic and Clinical characteristics of subject with SCD and controls.

Variable	SCD N = 100 mean \pm SD	Control N = 100 mean \pm SD	P-value
Age (years)	20.9 \pm 5.8	22.3 \pm 3.3	0.06
Male gender (%)	57(57)	55(55)	0.4
HR (bpm)	94.7 \pm 8.9	83.4 \pm 10.8	<0.001
Systolic BP (mmHg)	103.66 \pm 10.2	105.74 \pm 12.5	0.09
Diastolic BP (mmHg)	69.34 \pm 7.9	71.94 \pm 7.2	0.01
Weight (kg)	44 \pm 15	53 \pm 12	<0.001
Height (m)	1.56 \pm 0.11	1.63 \pm 0.51	<0.001
BMI (Kg/m)	18.1 \pm 3.6	22.7 \pm 2.2	<0.001
Hb (g/dl)	7.2 \pm 0.94	11.99 \pm 9.6	<0.001

Key: HR; heart rate, BP; blood pressure, BMI; body mass index, Hb; haemoglobin.

Table 2. Echocardiographic parameters of subjects with SCD and controls.

Variables	SCD N = 100 mean \pm SD	Controls N = 100 mean \pm SD	P value
AOD (mm)	24.3 \pm 3.1	24.8 \pm 3.7	0.6
LA (mm)	37.7 \pm 4.6	33.9 \pm 3.1	<0.001
LVEDD (mm)	47.1 \pm 7.9	43.9 \pm 5.3	0.001
LVESD (mm)	30.1 \pm 5.7	28.3 \pm 5.1	0.03
IVSTd (mm)	8.2 \pm 1.4	7.9 \pm 1.2	0.2
LVPWTd (mm)	9.3 \pm 1.5	8.1 \pm 1.1	0.001
EF (%)	58.9 \pm 4.8	60.1 \pm 5.1	0.3
LVM (g)	223.5 \pm 72.1	175.6 \pm 44.1	0.01
E (m/sec)	87.8 \pm 13.8	86.1 \pm 12.1	0.3
A (m/sec)	56.2 \pm 16.5	50.5 \pm 16.1	0.02
DT (ms)	186.5 \pm 53.2	240.6 \pm 54.8	0.02
E/A	1.67 \pm 0.55	1.77 \pm 0.69	0.3
IVRT (ms)	68.3 \pm 16.2	64.8 \pm 21.5	0.4

Key: AOD; aortic diameter, LAD; left atrial diameter, LVEDD; left ventricular end-diastolic dimension, LVESD; left ventricular end-systolic dimension, IVSTd; interventricular septal thickness in diastole, LVPWTd; left ventricular posterior wall thickness in diastole, EF; ejection fraction, FS; fractional shortening, LVM; left ventricular mass, E; early diastolic filling velocity, A; late diastolic filling velocity, DT; deceleration time, E/A; ratio of peak velocities, IVRT; isovolumic relaxation time.

Pattern of LV diastolic dysfunction among subjects with SCD and Controls.

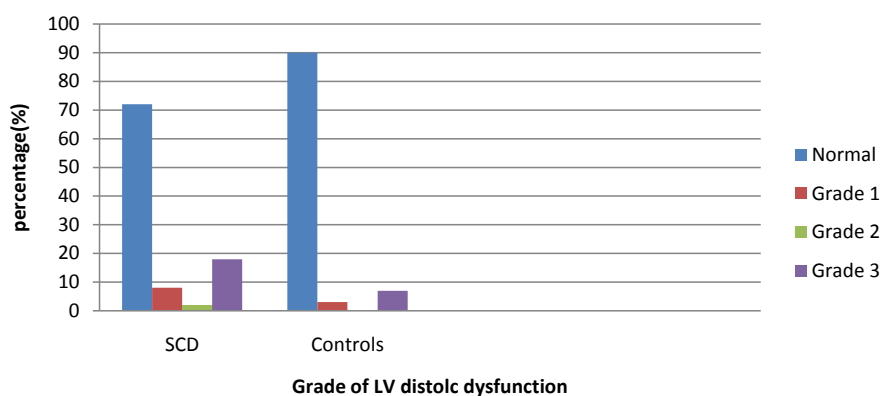


Figure 1. Pattern of Left ventricular diastolic dysfunction among subjects with Sickle cell disease and Controls.

4. Discussion

This echocardiographic study evaluates systolic and diastolic function in patients with sickle cell disease. In this study, the left atrial and left ventricular internal dimensions, wall thickness and LV mass were significantly increased in SCD patients, though LV ejection fraction was similar in both groups. This finding is in keeping with findings from previous studies [13] [14] [15] [16]. The ventricular

enlargement and hypertrophy is compensatory mechanisms for the long standing volume overload. These cardiac changes are needed in patients with chronic anaemia to increase the cardiac output, with little increase in heart rate.

Left ventricular diastolic dysfunction, was however common in the SCD subjects. Up to (28) 28% had some form of LV diastolic dysfunction. These finding also agrees with earlier studies of Doppler filling abnormalities [16] [17] [18] [19] [20]. While some studies reported lower prevalence of LV diastolic dysfunction among SCD patients, our finding is in keeping with what was reported by Abdul-Mohsen *et al*, among Saudi patients with SCD [15]. The diastolic relaxation of the left ventricle was significantly decreased in the SCD group, which resulted in a longer time for the rapid filling of that chamber. This abnormal diastolic relaxation can be secondary to decreased ventricular compliance or an impaired left ventricular contractile state. Preload, myocardial ischaemia or atrial contraction may all play a significant role in the observed ventricular diastolic filling. Although the exact mechanisms of abnormal diastolic function in SCD are uncertain, it is most likely caused by left ventricular hypertrophy and by increase in the left ventricular mass. Recurrent myocardial damage from vascular vaso-occlusive disease and iron overload [17]. The occurrence of LV diastolic dysfunction, however, may be considered an adverse prognostic factor for increased mortality [4] [17] [21].

5. Conclusion

Cardiac abnormalities including LV diastolic dysfunction are a common feature of SCD and are an important cause of morbidity and mortality associated with the disease. Therefore adolescents and adults with SCD should have routine echocardiographic studies performed as part of their medical care, to identify high-risk patients who may require additional treatment.

6. Study Limitations

Although mitral valve annular velocities can be used to draw inference about LV relaxation and LV filling pressure, tissue doppler imaging (TDI), is at the forefront in transthoracic echocardiographic assessment of LV diastolic dysfunction as it is less hindered by preload dependency. Mitral flow indices are very sensitive to preload conditions and may appear 'falsely normal' when preload is increased [22] [23] [24]. Facility for TDI was not available and therefore not used. Our study might thus have underestimated the prevalence of diastolic dysfunction in these patients.

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