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Left Ventricular Diastolic Function in Sickle Cell Anaemia: Clinical and haemodynamic Correlates

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Left ventricular diastolic dysfunction is an independent risk factor for mortality in sickle cell disease but the clinical and haemodynamic determinants of this complication are unknown.
Aims and Objectives: This study was aimed at evaluating the clinical and haemodynamic factors associated with left ventricular diastolic dysfunction in adult Nigerian sickle cell anaemia patients.
Methods: Trans-mitral Doppler echocardiography was used to assess left ventricular diastolic function in a study sample of 60 adult sickle cell anaemia patients and 60 normal age and sex matched controls. Diastolic function indices measured include: left atrial dimension, velocities of E

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and A waves, isovolumic relaxation time, E- wave deceleration time and pulmonary venous flow velocity curve analysis.

Results: The sickle cell patients had higher trans-mitral E- wave and A- wave velocities, reduced E/A ratio, as well as prolonged deceleration time of the E- wave and isovolumic relaxation time (IVRT)which are suggestive of impaired left ventricular compliance. Left ventricular diastolic dysfunction (defined as trans-mitral E/A ratio < 1) was demonstrated in 13.3% of the patients and in none of the normal control subjects. Significant correlations were found between indices of left ventricular diastolic function and age, haematocrit, body surface area and some blood pressure indices.

Conclusion: A significant proportion of steady state adult sickle cell anaemia patients presents with impaired left ventricular diastolic function. Disease duration, body surface area, blood pressure indices and haematocrit are notable clinical correlates of left ventricular diastolic function in sickle cell anaemia.

Keywords: Ventricular; diastolic; dysfunction; sickle cell; anaemia.

1. INTRODUCTION

Left ventricular diastolic dysfunction implies an impairment of left ventricular filling at normal left atrial pressure [1]. “The haemodynamic abnormality for left ventricular diastolic dysfunction is attributable to the combined effects of reduced left ventricular relaxation and alteration in left ventricular chamber compliance that are often observed in patients with left ventricular hypertrophy, cardiomyopathy, myocardial ischaemia, systemic hypertension as well as in normal aging” [2-6].

“A number of studies using standard Doppler parameters andtissue Doppler technique have identified diastolic dysfunction as a common finding in patients with sickle cell anaemia” [7,8,9]. “This complication has been found to be an independent risk factor for mortality with a risk ratio of 4.8” [10]. Considering the poor prognostic impact of left ventricular diastolic dysfunction in sickle cell anaemia, there is a growing interest in the evaluation of the clinical determinants of this complication. This study was aimed at assessing the clinical and haemodynamic factors associated with left ventricular diastolic dysfunction in adult Nigerian sickle cell anaemia patients as seen in the University of Nigeria teaching hospital Enugu, Nigeria.

2. METHODS

We conducted a cross sectional study on 60 sickle cell anaemia patients recruited through a systematic random sampling technique from attendees at the adult sickle cell clinic of the University of Nigeria Teaching Hospital (UNTH) Ituku–Ozalla, Enugu Nigeria. Patients enrolled for the study were adults (age ≥18 years) [11] who had haemoglobin genotype SS on haemoglobin electrophoresis, were in steady state and consented to participate in the study.

Steady state was defined as absence of any crisis or any symptoms/signs attributable to acute illnessin the preceding four weeks.An equal number of age and sex matched normal subjects served as controls. Exclusion criteria for the study include: history of use of tobacco, presence of congenital or acquired heart disease, excessive use of alcohol (i.e. more than 16gm of alcohol daily) [12], history of drug addiction, diabetes mellitus, hypertension, pregnancy, renal failure, presence of other forms of haemoglobinopathies.

“All the participants were evaluated with clinical examination and echocardiography. Clinical data obtained include: age, gender, body mass index, body surface area, crisis and blood transfusion frequencies and blood pressure indices. Total systemic resistance index was calculated as the ratio of mean arterial blood pressure and cardiac index and is expressed as dynes.sec/cm^5/m^2” [13,14]. “Echocardiography was done using Hewlett Packard Sonos 2500 echocardiography machine with 3.7MHz transducer. Echocardiographic measurements were taken in the standard positions as recommended by the American Society of Echocardiography” [15,16]:

Pulsed wave Doppler echocardiography was used to assess left ventricular diastolic function by the analysis of trans-mitral flow recordings from the cardiac apex. Measures of diastolic function evaluated include: Velocities of E and A waves, isovolumic relaxation time, and E- wave deceleration time. Additionally, Pulmonary venous flow velocity curve analysis was also used to assess left ventricular diastolic dysfunction by Doppler echocardiography [17]. The normal velocity curves consist of systolic and diastolic forward flow and reversed flow at atrial contraction, termed S, D and A respectively.The presence of reverse trans-mitral diastolic flow velocity was diagnostic of diastolic dysfunction. This finding was corroborated by the presence of inversion of the S/D flow in the pulmonary vein.

2.1 Data Analysis

Data were presented as means ± standard deviation for continuous variables and as proportions for categorical variables. Comparison of continuous variables between the sickle cell disease patients group and the control group were made with independent Student's t-test. For discrete variables distribution between groups were compared with Chi- square test and Fishers exact test as appropriate (where an expected cell is less than 5). Multivariate Pearson's correlation coefficient was used to determine the relations between clinical and echocardiographic data. In order to examine the effect of anaemia on the variables, the subjects were classified based on the haematocrit values into four classes in accordance with the World Health Organization classification of anaemia as follows:- Class 1; normal (haematocrit ≥ 36%), Class 2; mild anaemia (haematocrit 30-35.9%), Class 3; moderate anaemia (haematocrit 21 - 29.9%), Class 4; severe anaemia (haematocrit 18-20.9%) [18]. Inter-class differences in clinical and echocardiographic parameters in the patients were compared by one-way analysis of variance and post hoc multiple comparison of mean using the Tukey's honestly significant difference test. Intra-class differences in parameters between patients and controls in the same haematocrit class were analyzed using the independent Student's t-test. The relationship between clinical and echocardiographic variables while controlling for the effect of anaemia (haematocrit) was examined using the partial correlation analysis. All statistical analyses were carried out using the Statistical Packages for Social Sciences (SPSS Inc. Chicago Illinois) software version 25. Statistical tests with probability values less than 0.05 were considered statistically significant.

3. RESULTS

Data from a total of sixty sickle cell anaemia patients (30 males, 30 females) and sixty normal controls matched for age and sex were analyzed. The sample characteristics and baseline data are shown in Tables 1 and 2. The mean ages for patients and controls were 28.27±5.58 (range 18 - 44) and 28.37±5.91 (range 18 – 45) years respectively. There were no significant age and gender differences in patients and controls. The study group had higher E- wave and A- wave velocities, reduced E/A ratio, as well as prolonged deceleration time of the E- wave and isovolumicrelaxation time (IVRT); (Table 3). E/A ratio less than one was seen in 8(13.3%) of the study subjects and none (0%) in the control group; (χ^2= 8.571; P= 0.003), (Table 3). These findings were corroborated by the appearance of inversion of the S/D flow in the pulmonary vein. The gender difference in occurrence of reverse trans-mitral flow velocity (3 males; 5 female) was not statistically significant. Analysis of measures of left ventricular diastolic function in the three categories of haematocrit values in the patients shows significant progressive reduction in the left ventricular diastolic function indices with decreasing haematocrit levels, (Table 4).

However, intra-class comparison of echocardiographic parameters in subsets of patients and controls with similar haematocrit levels between 30 and 35.9% showed significant differences in the trans-mitral E/A ratio ratio (1.36±0.12) and 1.58±0.25 respectively; t=2.41; p=0.0267)), trans-mitral E-wave deceleration time (0.187±0.032 and 0.159±0.021seconds respectively; t=2.394, p<0.0278) and isovolumic relaxation time0.081±0.12 and 0.071±0.008 seconds respectively; t=2.230.p=0.0387, (Table 5).

Significant correlations were also noted between indices of left ventricular diastolic function and age, haematocrit, body surface area and some blood pressure indices; (diastolic blood pressure, mean arterial blood pressure and total systemic resistance index, Table 6).

4. DISCUSSION

In this case-control study on our sample population of steady state adult sickle cell anaemia patients, left ventricular diastolic function was significantly reduced in the patients compared with the controls. Impaired ventricular relaxation determined by reverse trans mitral filling velocities, (E/A ratio < 1) was found in 13.3% of the patients and none of the controls. This finding and the observation of prolongation of the

Table 1. Age, gender and anthropometric data

Parameters	Patients Mean (SD)	Controls Mean (SD)	T-Test	P-Value
Age (years)	28.27 (5.58)	28.37(5.91)	0.987	0.924
Gender {frequency(%)}			0.000	1.00[a]
Male	30(50)	30(50)		
Female	30(50)	30(50)		
Total	60	60		
Weight(kg)	54.97 (10.61)	67.35(8.37)	7.20	< .001*
Height(m)	1.62(0.14)	1.72(0.07)	4.960	< .001*
Body surface area(m^2)	1.62(0.03)	1.78(0.14)	3.723	< .001*
Body mass index(Kg/m^2)	20.47(2.73)	23.87(3.22)	6.181	< .001*

**Statistically significant. [a]Chi-square*

Table 2. Pulse and Blood pressure indices

Parameters	Patients Mean (SD)	Controls mean (SD)	T-test	P-value
Pulse rate (beat/min)	87.68 (8.91)	72.13 (6.79)	11.062	< .001*
Systolic BP(mmHg)	119.50 (11.70)	121.2 (8.97)	0.527	0.599
Diastolic BP(mmHg)	64.867 (8.95)	76.88 (6.18)	8.629	< .001*
Pulse pressure (mmHg)	54.63 (12.87)	44.31 (10.91)	4.735	0.001*
Mean arterial BP(mmHg)	81.18 (12.65)	91.71 (5.47)	5.850	< .001*
Haematocrit(%)	24.07 (3.10)	38.65 (1.97)	30.589	< .001*

**Statistically significant, BP=Blood pressure.*

Table 3. Comparison of left ventricular diastolic function in patients and controls

Parameters	Mean (SD)		T-test	P-value
	Patients	Controls		
Left Ventricular Mass Index (gm/m^2)	132.60(14.71)	75.17 (4.09)	7.294	< .0001*
Cardiac Index (L/mm/m^2)	4.43(1.15)	3.15(0.33)	6.378	< .0001*
TSRI (dynes.sec. $cm^{-5}.m^2$)	18.33 (2.27)	29.11(1.57)	30.254	<.0001*
E-wave velocity (cm/s)	81.30.(3.18)	73.22(9.26)	6.392	<.0001*
A wave velocity (cm/sec)	64.23 (6.81)	45.24(7.66)	14.367	<.0001*
E/A ratio	1.27(0.20)	1.62 (0.23)	8.895	<.0001*
E/A ratio < 1 {frequency (%)}	8 (13.3)	0(0)		0.003*[a]
IVRT (sec)	0.086(0.016)	0.078 (0.015)	3.1729	0.0019*
EDT (sec)	0.190(0.03)	0.179 (0.01)	2.694	0.0081*

*KEY: *Statistically significant, [a] – Fishers exact test, IVRT= isovolumic relaxation time, EDT= E-wave deceleration time*

declaration time of the E-wave demonstrated in the patients are consistent with left ventricular diastolic dysfunction. The finding of abnormal pulmonary venous flow pattern in these patients with reverse E/A ratio further supports the presence of significant diastolic dysfunction in the patients with sickle cell anaemia.

"Previous studies employing invasive right heart catheterization measurements in patients with pulmonary hypertension showed evidence of diastolic dysfunction in approximately one-half of the patients" [19,20]. "Screening echocardiography studies however, show a significant variation in the prevalence of diastolic dysfunction. The discrepancy is due to the well-known difficulty in the noninvasive diagnosis of diastolic dysfunction" [15,16,17].

Adebayo and Balogun [21] reported observations of reverse E/A ratio in 10 (24.4%) of steady state sickle cell anaemia patients studied. However, unlike in the study by Adebayo and Balogun [21] where 19.5% of the patients had restrictive flow pattern, restrictive pattern of flow

Table 4. Left ventricular diastolic function in sickle cell patients in relation to haematocrit levels

Parameters	Values; mean (SD)			F-Statistic	P-Value
	Haematocrit levels				
	Mild(n=9)	Moderate (n=40)	Severe (n=11)		
LVMI(gm/m^2)	121.28(15.64)	132.78(21.47)	181.21(32.23)	22.482	<.0001*
CI (L/mm/m^2)	4.64(1.29)	4.14(1.13)	5.29(1.75)	3.617	0.033*
E-wave(cm/sec)	81.85(10.94)	80.62(14.28)	79.50(7.25)	1.201	0.308
A-wave(cm/sec)	60.25(7.67)	64.07(10.80)	67.07(6.66)	1.647	0.202
E/A ratio	1.36(0.12)	1.26(0.11)	1.19(0.16)	4.855	0.011*
IVRT(sec)	0.081(0.012)	0.087(0.006)	0.090(0.010)	3.519	0.036*
EDT(sec)	0.187(0.012)	0.191(0.015)	0.204 (0.016)	4.136	0.021*

*KEY:*Statistically significant, CI=Cardiac index, LVMI=Left ventricular mass index, IVRT= isovolumic relaxation time, EDT= E-wave deceleration time.*

Table 5. Comparison of echocardiographic parameters in subsets of patients and controls with haematocrit levels between 30 and 35.9%

Parameters	Values; Mean(SD)		T-Test	P-Value
	SCA (n=9)	Controls (11)		
LVMI(gm/m^2)	121.28(32.01)	73.80(13.79)	4.147	0.002*
EDT(sec)	0.187(0.032)	0.159(0.02)	2.394	0.0278*
E/A ratio	1.36(0.12)	1.58(0.25)	2.414	0.0267*
IVRT(sec)	0.081(0.012)	0.071(0.008)	2.230	0.0387*
CI(L/mm/m^2)	4.47(1.12)	2.57(0.47)	5.125	0.0001*

*KEY: *Statistically significant, SCA= sickle cell anaemia, CI=Cardiac index, LVMI=Left ventricular mass index, IVRT= isovolumic relaxation time, EDT= E-wave deceleration time.*

Table 6. Correlates of Left ventricular diastolic function indices

		IVRT	EDT	EDV	A-Wave	E-Wave	E/A-ratio
Age	Correlation	.053	.115	-.041	.311*	-.032	-.381*
	Sig.	.686	.375	.752	.014	.802	.002
Pulse rate	Correlation	-.046	-.115	-.026	.106	.187	.034
	Sig.	.723	.373	.843	.413	.146	.796
Systolic Blood Pressure	Correlation	.170	-.201	-.304*	-.022	.104	.093
	Sig.	.190	.117	.016	.864	.420	.473
Weight	Correlation	.131	-.114	.013	-.026	-.106	-.050
	Sig	.313	.378	.921	.844	.414	.701
Body Mass Index	Correlation	.108	-.205	.059	-.101	-.122	.008
	Sig.	.406	.111	.647	.435	.344	.949
Diastolic Blood Pressure	Correlation	.371**	.280*	-.151	-.026	.000	.113
	Sig.	.003	.028	.242	.839	.999	.380
Body Surface Area	Correlation	-.006	-.120	-.100	-.204	.090	.252*
	Sig.	.966	.354	.438	.112	.485	.048
Mean Arterial Blood Pressure	Correlation	.095	-.069	-.391**	.125	.177	.195
	Sig	.465	.596	.002	.335	.169	.130
Haematocrit	Correlation	.059	.014	-.004	-.052	-.095	.335*
	Sig.	.651	.912	.976	.689	.462	.026
Total Systemic Resistance Index	Correlation	.340**	.252*	.461**	-.031	.091	.132
	Sig.	.007	.048	.000	.811	.481	.308
Crisis Frequency	Correlation	-.025	-.207	.341	-.036	.038	-.005
	Sig	.846	.107	.007	.780	.768	.970
Transfusion Frequency	Correlation	-.053	.007	.144	-.139	-.153	.037
	Sig	.683	.960	.256	.280	.235	.774

was not observed in any of the patients in this study. The reason for this difference is not obvious but it has been postulated that recurrent micro-infarct resulting in scar tissue formation in the ventricle might be responsible for impaired ventricular compliance with a restrictive pattern [21]. Lewis et al demonstrated that a high prevalence of early left ventricular filling abnormalities were evident with Doppler echocardiography in 57% of 30 patients with sickle cell anaemia even in the absence of symptoms of heart failure [22].

We observed a significant correlation of diastolic abnormalities with advancing age, body surface area, haematocrit levels and increasing blood pressure indices. Multi-factorial mechanisms have been postulated to play roles in the pathogenesis of diastolic abnormalities in sickle cell disease. These include: compensatory hypertrophy secondary to anaemia, left ventricular dilatation along with a systemic vasculopathy affecting afterload, direct myocardial damage from micro-vascular disease and iron deposition [23,24,25]. "Although systemic blood pressure in sickle cell disease is known to be lower than in control subjects, the presence of relative systemic hypertension in these patients has been linked with renal dysfunction and adverse outcomes" [26,27,28,29]. "In addition, there are significant associations between systolic blood pressure and both increased pulmonary pressures and left ventricular filling pressures" [26,30]. The sickle cell patients recruited in this study were all normotensive. However, we observed significant correlation between rising diastolic blood pressures and (1) end-diastolic time and (2) isovolumic relaxation time on echocardiography. Increasing systolic blood pressure and mean arterial blood pressure negatively correlated with end diastolic volume. Diastole has been traditionally divided into the isovolumic relaxation phase and the filling phase. The filling phase is divided into the early filling phase, diastasis and period of atrial systole. The isovolumic relaxation time (time interval from the aortic valve closure to mitral valve opening) in this study significantly correlated with diastolic blood pressure and the total systemic resistance index. All these findings corroborate the known potentially adverse impact of even mildly elevated blood pressure indices on cardiovascular function in patients with sickle cell anaemia.

The impact of age on diastolic function in this study is noteworthy. Age is related to disease duration and with the current improved awareness and management of sickle cell disease many of these patients live longer to develop diastolic dysfunction and other cardiac complications.

We endeavored to explore the relationship between diastolic function and clinical variables such as crises and blood transfusion frequencies as measures of disease severity. Our study found no relationship between these variables. This observation should however, be interpreted on the understanding that the information was based on patients' historical recall abilities rather than documented data.

Obesity adversely impacts cardiovascular risk factors as well as left ventricular structure and function. Body mass index (BMI) and Body surface area(BSA) are common measures of body habitus used for indexing haemodynamic physiologic parameters. Although increase in body mass is recognized as a major determinant of left ventricular diastolic function [27], this relationship was not observed in our study population probably due to the absence of over-weight individuals in the study sample.

We observed a strong correlation between BSA and left ventricular diastolic function. Various investigators have also noted the influence of body surface area on the dimensions and thickness of cardiac structures [28,29]. "Body surface area correlates more closely to physiologic parameters than body weight and it is commonly used in medicine, in research and clinical practice, as a biometric unit to adjust size, mass and volume, in individuals with heart failure at different body sizes [31,32], and has also been shown to be an outcome predictor better than other measures of body habitus and irrespective of height correction" [33,34,35].

Haemodynamic changes secondary to anaemia play significant roles in the pathogenesis of left ventricular dysfunction in sickle cell anaemia. As expected, this explains the significant progressive reduction in the left ventricular diastolic function indices with decreasing haematocrit levels in our study patients as well as the negative correlation between haematocrit and trans-mitral E/A ratio. Even among subjects with comparable haematocrit levels some degree of diastolic dysfunction persisted in sickle cell patients. These findings suggest that background chronically impaired diastolic function might be present in these patients which tends to deteriorate with declining red blood cell volume.

5. CONCLUSION

A significant proportion of steady state adult sickle cell anaemia patients presents with impaired left ventricular diastolic function. Disease duration, body surface area, blood pressure indices and haematocrit level are notable clinical correlates of left ventricular diastolic function in sickle cell anaemia.

CONSENT AND ETHICAL APPROVAL

Ethical clearance for the study was obtained from the Health and Ethics Committee of University of Nigeria Teaching Hospital Enugu. Prior informed consent was obtained from all the participants in the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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