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Echocardiographic findings in adult Nigerian sickle cell patients with cardiovascular autonomic dysfunction

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ABSTRACT

Introduction: Involvement of the cardiovascular autonomic nervous system in various diseases is often associated with increased morbidity and mortality.
Aim: This study was aimed at determining the relationship between cardiovascular autonomic dysfunction (CAD) and echocardiographic indices of cardiac function in adult Nigerian sickle cell anaemia patients.
Material and methods: A cross sectional study was done using 62 sickle cell anaemia patients and 62 age and sex matched normal controls. CAD was determined based on abnormal values in at least two of five non-invasive tests: Valsalva manoeuver, heart rate variation during deep breathing, heart rate response to standing, blood pressure response to sustained hand grip, and blood pressure response to standing. The subjects were subsequently evaluated with echocardiography.
Results and discussion: Significant increases in left ventricular posterior wall thickness, left ventricular mass as well as left ventricular mass index were found in patients with CAD. Indices of left ventricular diastolic and systolic functions were comparable in patients with and without CAD, however patients with CAD had lower peak aortic systolic velocity ($P = 0.038$). Valsalva ratio correlated significantly with right ventricular internal diameter ($r = -0.388$; $P = 0.009$), left ventricular posterior wall diameter ($r = -0.352$; $P = 0.019$), left ventricular end systolic stress/end systolic dimension ratio ($r = 0.512$; $P < 0.001$), and pulmonary artery flow acceleration time ($r = 0.499$; $P = 0.001$).
Conclusions: CAD is a serious complication of sickle cell anaemia. All the patients should be routinely evaluated for CAD.

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1. Introduction

Involvement of the cardiovascular autonomic nervous system in various diseases is often associated with increased morbidity and mortality. Orchard et al.[1] studied a population-based sample of individuals with type 1 diabetes. Initial analysis based on a 2-year follow-up of 487 subjects revealed a four-fold higher mortality rate in individuals with cardiac autonomic neuropathy at baseline compared with individuals without it.

The relationship between cardiovascular autonomic neuropathy and the subsequent incidence of fatal or non-fatal cardiovascular events, defined as myocardial infarction, heart failure, resuscitation from ventricular tachycardia or fibrillation, angina, or the need for coronary revascularization was assessed in two prospective studies.[2,3] The relative risks associated with cardiovascular autonomic neuropathy in these studies were 2.2 and 3.4, respectively, with the latter result just achieving statistical significance ($P < 0.05$).

In spite of the relatively high prevalence of sickle cell disease in Nigeria as well as the significant negative impact of cardiovascular autonomic dysfunction (CAD) on the survival and quality of life in individual with various disease conditions, there has been no published report known to the authors assessing the cardiac changes associated with CAD in Nigerian sickle cell anaemia patients.

2. Aim

This study was carried out to determine relationship between CAD and echocardiographic indices of cardiac function in adult Nigerian sickle cell anaemia patients, as seen at the adult out-patients sickle cell anaemia clinic of the University of Nigeria Teaching Hospital (UNTH) in Enugu, Nigeria.

3. Material and methods

3.1. Study design

A cross sectional study was conducted on 62 steady state sickle cell anaemia patients (aged ≥18 years) and 62 age and sex matched normal controls from February to August 2007. Steady state is defined as absence of any crisis or blood transfusion in the preceding four weeks, absence of any symptoms or signs attributable to acute illness. The patients were drawn from the adult out patients sickle cell clinic of the University of Nigeria Teaching Hospital in Enugu. All the subjects were assessed for cardiovascular autonomic function as well as clinical and echocardiographic evaluation.

3.2. Cardiovascular autonomic function test

Cardiovascular autonomic function test was assessed using five simple tests: (1) Valsalva manoeuver, (2) heart rate variation during deep breathing, (3) heart rate response to standing, (4) blood pressure response to sustained hand grip, and (5) blood pressure response to standing. The procedures were first demonstrated and rehearsed with the subjects before the actual measurements were made. A diagnosis of CAD was made based on abnormal values for at least two of the above tests. The detailed procedures for evaluation of cardiovascular autonomic function had been previously reported.[4]

3.3. Echocardiography

The subjects were subsequently booked for further evaluation with echocardiography. Echocardiography was done using Hewlett Packard Sonos 2500 echocardiographic machine with 3.7 mHz transducer which has capacity for M-mode, 2-dimensional and colour Doppler studies. The following measurements were taken in the standard positions as recommended by the American Society of Echocardiography[5,6]: Left atrial dimension, aortic root dimension, transmitral E and A wave velocities, isovolumic relaxation time, E-wave deceleration time, left ventricular (LV) end diastolic diameter, LV end systolic diameter, ventricular septal wall thickness, posterior wall thickness, fractional shortening (determined by difference between end diastolic diameter and end systolic diameter divided by end diastolic diameter), LV mass, and LV mass index (derived by dividing LV mass by body surface area), end diastolic volume, end systolic volume stroke volume, cardiac output, cardiac index, velocity of circumferential shortening, and systolic time intervals. LV end systolic stress (LVESS) was calculated using the formula[7]:

$$\mathrm{LVESS} = \frac{0.334 \times \mathrm{P} \times \mathrm{LVESD}}{\mathrm{LVPWTs} \times \mathrm{I} \times \mathrm{LVPWTs/LVESD}}$$

The value is expressed in kdyn·cm^{-2}, where P is the cuff systolic brachial artery pressure in mmHg, LVPWTs is the end systolic posterior wall thickness and LVESD is LV end systolic diameter.

3.4. Ethical consideration

Ethical clearance for the study was obtained from the Ethical Committee of UNTH, Enugu, Nigeria. All the participants were treated in accordance with the requirements of good clinical practice. The Declaration of Helsinki's recommendations for guiding physicians in biomedical research involving human subjects were followed.[8]

3.5. Data analysis

Data were presented as both means and standard deviations (SD) for continuous variables or percentages for discrete variables. Differences between means for sickle cell disease patients group and control group were compared with the independent Student's t-test.

For discrete variables, distributions between groups were compared with χ^2 test and Fishers exact test as appropriate. Multivariate Pearson's correlation coefficient analysis was used to evaluate relationship between CAD and echocardiographic variables.

All statistical analyses were conducted using the statistical packages for social sciences (SPSS Inc. Chicago, IL) software version 11.0. Statistical tests at 95% confidence interval with P values less than 0.05 were considered statistically significant.

Table 1 – Baseline clinical characteristics in patients with and without CAD.

Parameters	CAD^+ mean ± SD	CAD^- mean ± SD	t-test	P value
Age, years	28.3 ± 5.8	28.0 ± 4.9	0.233	0.817
Gender, %				
Male	23 ± 52.3	8 ± 44.4	0.08	0.780[a]
Female	21 ± 47.7	10 ± 55.6		
Total	44	18		
Weight, kg	53.8 ± 11.6	58.2 ± 6.4	1.890	0.064
Height, m	1.6 ± 0.2	1.7 ± 0.1	1.749	0.086
Body surface area, m^2	1.6 ± 0.3	1.6 ± 0.1	0.223	0.825
Body mass index, kg/m^2	20.4 ± 2.9	21.0 ± 2.1	0.982	0.331
Haematocrit	23.46 ± 2.96	26.00 ± 2.91	3.099	0.004*

CAD^+ – patients with CAD; CAD^- – patients without CAD.
[a] χ^2 test.
* Statistically significant.

4. Results

4.1. *Baseline clinical characteristics*

The sex distribution of CAD was 23 (52.3%) and 21 (47.7%) respectively in males and females. The mean ages were 28.3 ± 5.8 years for patients with CAD and 28.0 ± 5.0 years for patients without CAD ($t = 0.23$; $P = 0.817$). There were no statistically significant differences in the anthropometric variables in patients with CAD when compared with those without CAD. Sickle cell anaemia patients with CAD had significantly lower haematocrit level than patients without CAD (Table 1).

4.2. *Echocardiographic findings in CAD*

4.2.1. *Cardiac dimensions*

The M-mode and 2-dimensional echocardiographic measurements are shown in Table 2. Significant increases in LV posterior wall thickness, LV mass as well LV mass index were found in patient with CAD.

4.2.2. *Left ventricular function*

Indices of LV diastolic and systolic functions were comparable in patients with and without CAD, however patients with CAD had lower peak aortic systolic velocity ($P = 0.038$; Tables 3 and 4).

4.2.3. *Correlation of various cardiovascular autonomic function tests with electrocardiographic and echocardiographic variables in patients with CAD*

Cardiovascular autonomic function tests showed some correlations with echocardiographic indices as seen in Table 5. The valsalva ratio correlated significantly with right ventricular (RV) internal diameter ($r = -0.388$; $P = 0.009$), LV posterior wall diameter ($r = -0.352$; $P = 0.019$), LV end systolic stress and LV end systolic diameter ratio ($r = 0.512$; $P < 0.001$), and pulmonary artery flow acceleration time ($r = 0.499$; $P = 0.001$).

Table 2 – Echocardiographic parameters in patients with and without CAD.

Parameters	CAD^+ mean ± SD	CAD^- mean ± SD	t-test	P value
Aortic root dimension, cm	2.89 ± 0.396	2.88 ± 0.251	0.071	0.944
Left atrial dimension, cm	4.19 ± 0.890	4.37 ± 0.374	1.106	0.273
Aortic cusp's excursion, cm	1.645 ± 0.578	2.30 ± 0.813	1.277	0.218
E-point to septal seperation, cm	0.829 ± 0.404	1.238 ± 0.923	0.894	0.383
EF slope, cm/s	11.18 ± 4.03	10.63 ± 4.31	0.473	0.638
PWD, cm	0.915 ± 0.372	0.753 ± 0.112	2.619	0.011
End diastolic dimension, cm	5.45 ± 0.551	5.67 ± 0.458	1.643	0.109
End systolic dimension, cm	3.45 ± 0.583	3.67 ± 0.776	1.071	0.294
Interventricular septum, cm	0.983 ± 0.325	0.856 ± 0.190	1.904	0.062
End diastolic volume, mL	132.87 ± 35.07	128. 28 ± 28.71	0.491	0.626
End systolic volume, mL	52.98 ± 25.28	49.10 ± 19.90	0.581	0.563
Cardiac out-put, L/min	7.02 ± 2.12	6.82 ± 1.17	0.481	0.632
LV mass, gm	209.27 ± 41.62	170.99 ± 36.34	2.356	0.022*
PACT, s	0.130 ± 0.021	0.110 ± 0.011	1.076	0.288
TSR, $kdyne{\cdot}s{\cdot}cm^{-5}\,m^{-2}$	21.0 ± 9.68	19.74 ± 5.12	0.668	0.507
LV mass index, gm/m^2	134. 57 ± 65.70	102.74 ± 22.81	2.825	0.006*
PAP, mmHg	22.03 ± 9.40	21.57 ± 6.75	0.213	0.832
RVID, cm	2.28 ± 0.618	2.11 ± 0.571	1.032	0.306

CAD^+ – patients with CAD; CAD^- – patients without CAD; PWD – left LV posterior wall diameter in systole; PACT – pulmonary artery flow acceleration time; TSR – total systemic resistance index; PAP – pulmonary artery pressure; RVID – RV internal dimension.
* Statistically significant.

Table 3 – LV systolic function in patients with and without CAD.

Parameters	CAD+ve	CAD−ve	T-Test	P value
VCF, cm s^{-1}	1.389 ± 0.819	1.062 ± 0.369	0.957	0.343
FS, %	37.66 ± 8.89	34.04 ± 10.71	1.268	0.216
EF, %	61.33 ± 12.09	62.54 ± 8.91	0.455	0.666
CI, L/min/m^2	4.54 ± 1.71	4.18 ± 0.652	1.199	0.235
AoV_{max}, cm/s	134.00 ± 24.97	145.24 ± 15.54	2.314	0.038*
ESS, kdyne cm^{-2}	69.89 ± 7.51	77.99 ± 6.97	0.393	0.695
ESS/ESD ratio	19.61 ± 4.06	19.21 ± 2.80	0.089	0.929
PEP	0.0796 ± 0.019	0.0716 ± 0.016	1.690	0.100
ET	0.369 ± 0.085	0.333 ± 0.095	1.454	0.151
PEP/ET	0.215 ± 0.044	0.223 ± 0.0518	0.570	0.573

CAD^+ – patients with CAD; CAD^- – patients without CAD; VCF – velocity of circumferential shortening; FS – fractional shortening; EF – ejection fraction; CI – cardiac index; AoV_{max} – peak aortic systolic velocity; ESS – end systolic stress; ESD – end systolic dimension; PEP – pre-ejection time; ET – ejection time.
* Statistically significant.

Table 4 – Left ventricular diastolic function in patients with and without CAD.

Parameters	CAD^+ mean ± SD	CAD^- mean ± SD	t-Test	P value
E-wave velocity, cm/s	81.27 ± 21.44	81.07 ± 13.01	0.045	0.964
A-wave velocity, cm/s	54.44 ± 18.86	51.13 ± 14.37	0.748	0.459
E/A ratio	1.63 ± 0.80	1.62 ± 0.31	0.091	0.928
IVRT, s	0.131 ± 0.0110	0.161 ± 0.0238	0.501	0.622
EDT, s	0.123 ± 0.0376	0.124 ± 0.0276	0.128	0.899

CAD^+ – patients with CAD; CAD^- – patients without CAD; IVRT – isovolumic relaxation time; EDT – E-wave deceleration time.
*Statistically significant.

Table 5 – Correlation of cardiovascular autonomic function tests with echocardiographic parameters.

Echo-cardiographic parameters	Cardiovascular function tests				
	Valsalva ratio	HRV	30:15 ratio	Hand grip	Postural hypotension
RVID	$r = -0.388^{**}$	$r = 0.208$	$r = -0.329^{*}$	$r = 0.205$	$r = 0.104$
	$P = 0.009$	$P = 0.176$	$P = 0.029$	$P = 0.133$	$P = 0.502$
ESD	$r = -0.058$	$r = -0.432^{**}$	$r = 0.128$	$r = -0.196$	$r = 0.128$
	$P = 0.710$	$P = 0.003$	$P = 0.408$	$P = 0.203$	$P = 0.408$
PWD	$r = -0.352^{*}$	$r = -0.039$	$r = -0.241$	$r = -0.039$	$r = 0.161$
	$P = 0.019$	$P = 0.800$	$P = 0.114$	$P = 0.803$	$P = 0.296$
ESS/ESD	$r = 0.512^{**}$	$r = -0.066$	$r = 0.346^{*}$	$r = 0.020$	$r = -0.237$
	$P = 0.000$	$P = 0.669$	$P = 0.021$	$P = 0.899$	$P = 0.121$
FS	$r = 0.025$	$r = -0.328^{*}$	$r = -0.048$	$r = 0.055$	$r = -0.291$
	$P = 0.874$	$P = 0.030$	$P = 0.758$	$P = 0.724$	$P = 0.055$
PEP	$r = -0.147$	$r = -0.325^{*}$	$r = -0.164$	$r = -0.062$	$r = -0.044$
	$P = 0.341$	$P = 0.031$	$P = 0.287$	$P = 0.690$	$P = 0.778$
ET	$r = -0.149$	$r = -0.374^{*}$	$r = -0.133$	$r = 0.005$	$r = -0.009$
	$P = 0.334$	$P = 0.012$	$P = 0.390$	$P = 0.973$	$P = 0.956$
PACT	$r = 0.499^{**}$	$r = -0.130$	$r = 0.341^{*}$	$r = 0.044$	$r = -0.289$
	$P = 0.001$	$P = 0.398$	$P = 0.023$	$P = 0.778$	$P = 0.057$
EX	$r = -0.126$	$r = 0.195$	$r = 0.040$	$r = -0.299^{*}$	$r = 0.055$
	$P = 0.417$	$P = 0.206$	$P = 0.746$	$P = 0.049$	$P = 0.723$
AOV_{max}	$r = -0.196$	$r = -0.269$	$r = 0.133$	$r = -0.365^{*}$	$r = 0.245$
	$P = 0.203$	$P = 0.078$	$P = 0.390$	$P = 0.015$	$P = 0.110$

RVID – right ventricular internal diameter; ESD – end-systolic dimension; PWD – posterior wall thickness; ESS – end-systolic stress; FS – fractional shortening; PEP – pre-ejection period; ET – ejection time; PACT – pulmonary artery flow acceleration time; ES – aortic cusp's excursion; AOV_{max} – peak aortic systolic velocity.
* Statistically significant.

Significant negative correlations were found between diastolic blood pressure response to sustained hand grip and aortic cusp's excursion and peak aortic systolic velocity. Significant negative correlations were also demonstrated between heart rate variability and LV end systolic dimension, fractional shortening and ejection time. Heart rate response to standing showed significant negative correlation with RV internal diameter, and a positive

correlation with LV end systolic stress and end systolic dimension ratio.

5. Discussion

Previous studies have reported increased LV mass and LV wall thickness in sickle cell anaemia patients. These have been attributed to the hyperdynamic circulatory state secondary to chronic anaemia seen in sickle cell anaemia.[9–12]

In this study, sickle cell patients with CAD had significantly elevated LV mass, LV mass index and increased LV posterior wall thickness when compared with patients without CAD. Multiple factors are contributory to these observations. The most significant of these seems to be the cardiovascular impact of chronic anaemia. Our findings indicate that patients with CAD have significantly greater degree of anaemia (haematocrit 23.46%) compared with those without CAD (haematocrit 26.00%; $P = 0.04$). Additionally, the presence of significant degree of anaemia and the treatment thereof with multiple blood transfusions could precipitate secondary haemochromatosis and worsen cardiac remodelling and chamber enlargement.[13,14] It is postulated that this subset of sickle cell patients with severe anaemia and CAD might identify patients with advance disease and at increased risk of cardiac complications.

Besides, increased LV mass index has been increasingly recognized as an independent risk factor and predictor of adverse cardiovascular events.[15] Its association with CAD in patients with sickle cell anaemia might suggest significantly increased cardiac morbidity in these patients. In this study the exact role of haemolysis-induced increased iron turnover and haemochromatosis in the pathophysiology of the cardiac findings were not explored. However, these effects are not likely to be substantial given the fact that all the patients in this study sample were in steady state and potentially high risk patients who received blood transfusion in the preceding four weeks were excluded from the study.

Despite myocardial remodelling/hypertrophy, patients with sickle cell anaemia were reported to have increased myocardial wall stress as well as impaired ventricular relaxation.[16] Data from clinical studies evaluating LV systolic function using load-independent measures of myocardial contractility have revealed significant systolic dysfunction in sickle cell anaemia patients[17,18] Indices of LV systolic and diastolic function are known to be significantly reduced in sickle cell patients when compared with normal controls.[7,17,18] However, no significant differences were noted in these parameters in patients with and without CAD. No study was found in the literature for comparison of our observations on the echocardiographic findings in sickle cell patients with CAD. However, in a study of diabetic patients with and without CAD, Roy et al.[19] demonstrated a decreased cardiac output in response to exercise in individuals with CAD. This finding tends to suggest that systolic function might be impaired in patients with cardiovascular autonomic neuropathy. Our findings in this study of significant positive correlation of cardiovascular autonomic function test parameters with indices of LV systolic function appear to support the foregoing suspicion. This study demonstrated significant positive correlation between Valsalva ratio and 30:15 beat ratio on standing with end systolic stress and end systolic dimension ratio. The end systolic stress-dimension relationship is considered an index of contractile function independent of loading characteristics in patients with chronic anaemia, and studies have indicated significant decreases of this parameter in patients with sickle cell anaemia.[15,16] Additionally, heart rate variability on deep breathing correlated significantly with ejection phase indices of systolic function. These findings suggest the vital role of cardiovascular autonomic reflex in maintenance of systolic function.

6. Conclusions

In conclusion, CAD is a serious complication of sickle cell anaemia. All the patients should be routinely evaluated for early detection and management of this complication.

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