

Cardiovascular autonomic reflex Function in Sick Cell Anaemia Patients

6

Sanya EO, *Soladoye A, Olanrewaju TO, Kolo PM, *Durotoye I

Department of Medicine,

*Department of Haematology,

University of Ilorin Teaching Hospital Nigeria

*Department of Physiology

University of Ilorin Nigeria

Correspondence to

Emmanuel .O. Sanya,

PO Box 5314, Ilorin, Kwara State .

emanuelosanya@yahoo.com

Summary

Aims and objectives: Cardiovascular autonomic dysfunction (CAD) has been documented as part of neurological complications in sickle cell anaemia (SCA). There is little information on CAD from sub-Saharan Africa with 25-40% prevalence rate of sickle cell trait. This study therefore assessed cardiovascular autonomic reflex function in a group of Nigerians with SCA.

Subjects and methods: Forty SCA and 44 controls (Hemoglobin AA) were studied. They were assessed using 6 non-invasive cardiovascular autonomic reflex (CAR) tests. Parasympathetic functions were assessed with heart rate variability (HRV) to deep breathing, Valsalva maneuver and lying-to-standing test while sympathetic blood pressure regulation was assessed by systolic and diastolic blood pressure responses to lying-to-standing position and isotonic handgrip test.

Results: Mean haemoglobin (Hb) concentration of SCA patients and controls were 8.4 ± 2.4 g/dl and 13.1 ± 0.9 g/dl, respectively. Baseline heart rate was significantly faster in the SCA patients (84 ± 12 beats/minute) than in controls (76 ± 11 beats/minute) [$P < 0.05$]. Eleven SCA compared to 2 controls had abnormal responses to deep breathing test ($P = 0.003$); 15 SCA and 6 controls had impaired Valsalva ratio ($P = 0.01$); 8 SCA and 4 controls had abnormal responses lying-to-standing test ($P = 0.2$). Although, more SCA patients compared to controls had abnormal responses to sympathetic mediated blood pressure tests the difference was insignificant ($P > 0.05$). Overall 21 (53%) SCA patients compared to 4 control subjects (9%) fulfilled the criteria for cardiovascular autonomic neuropathy (presence of ≥ 3 CAR tests) with $p < 0.05$.

Conclusion: CAN occur in Nigerians with SCA with relative preservation of the sympathetic blood pressure reflex control compared to parasympathetic heart rate regulation. Increase baseline heart rate associated with SCA in the presence of chronic anaemia could result in myocardial hypertrophy and dilatation. This is likely to be predispose sicklers to hypoxia-related arrhythmia.

Key words: sickle cell anaemia - cardiovascular autonomic dysfunction

Introduction

Sickle cell disease (SCD) is an inherited multisystemic disorder that is caused by abnormality in hemoglobin synthesis¹. The homozygous state of the disease is referred to as sickle cell anaemia (SCA).

Derangements in cardiac structure and functions are common sequelae of SCA^{2,3}. These include cardiomegally that is related to increase workload from chronic anaemia, of arrhythmia and myocardial infarction³. The myocardial ischemia of SCA occurs in the background of normal coronary angiography and has uncertain pathogenesis⁴. Part of possible mechanisms that has been proposed includes combine effects of severe anaemia, microthrombi

and increased blood viscosity^{3,4}.

Myriad of neurologic complications have been documented in SCA^{1,5,6} with varied frequency from 25% to 76%⁵. Interest on effects autonomic nervous system dysfunction in SCA has increased recently with several publications released on this topic^{7,8}. Only few of these are from sub-Saharan Africa countries^{2,10}, despite the high prevalence rate of sickle cell gene of 25 to 40% in the region^{1,11}. Lack of facilities need to evaluate autonomic function might be partly responsible. This necessitated doing present study in which conventional clinical cardiovascular autonomic reflex (CAR) tests were used to evaluate autonomic function in a group of Nigerians with SCA. This non-invasive method have sensitivity of close

to 87%^{12,13} and has been used to establish cardiovascular autonomic neuropathy (CAN) in diabetes mellitus, heart failure, chronic renal failure, Parkinson's and alcoholic heart diseases^{12, 14-17}.

Subjects and methods

The patients included 40 sickle cell anaemic individuals (20 males and 20 females) with mean age of 24.9 ± 6.4 years. Patients were crises free 2 weeks prior to the evaluation and had not been transfused in the preceding 3 months. Forty-four (44) individuals with Hb AA genotype (21 males and 23 females) were selected as control subjects. Exclusion criteria included history of previous stroke, diabetes mellitus, hypertension, heart failure and chronic liver disease. Smokers and individuals that took alcoholic beverages of more than 3 bottles per week were excluded from the study. None of the study participants were on any medication such as beta blockers, nitrates or tricyclic antidepressants that could affect autonomic function. Willing SCA patients were encouraged to participate in the study. They were recruited from sickle cell clinic in medical outpatient department of the University of Ilorin Teaching Hospital, Ilorin, Nigeria. The controls were drawn from amongst medical students and members of staff of the hospital. All subjects gave informed consent and approval for the study was obtained from the Ethics Committee of the Institution.

Cardiovascular autonomic nervous function tests were performed in the morning in a quiet room after an initial 15 minutes rest. Thereafter a baseline ECG was performed in supine position. Initial test was done in order to train the subjects to perform the manoeuvre correctly. The protocol used for the autonomic test is as stated in previous published works^{12,13,16}. A standard test sequence was followed: Valsalva manoeuvre, deep breathing test, a lying-to-standing and sustained handgrip test. A period of 5 minutes rest was given after each test. Subjects had haemoglobin electrophoresis done to confirm their genotype. The ratio of longest R-R interval on ECG shortly after the Valsalva manoeuvre to the shortest R-R interval immediately after the strain period was calculated and expressed as the Valsalva ratio^{12,16}. Value of 1.4 or below was considered abnormal. The deep breathing test involved paced breathing at a rate of 6 deep breaths per minute. The difference in R-R interval on the ECG tracing during expiration (longest) and in inspiration (shortest) was calculated ($RR_{\text{Expiration}} - RR_{\text{Inspiration}}$). Value less than 1.2 was considered abnormal. The 30:15 ratio was the heart rate (HR) response from lying-to-standing position and was expressed as the ratio between the 30th and 15th R-R interval^{12,13}. Ratio less than 1.04 depicts impairment in the reflex function¹³. Cardiovascular autonomic neuropathy was defined as occurrence of 3 or more CAR tests^{9,12}. The ECG tracing was read manually by the same person. Blood pressure sympathetic reflex test was evaluated using systolic blood pressure (SBP) and diastolic blood pressure

(DBP) responses to change in posture from supine position to erect posture for minimum of 3 minutes¹³. Drop in SBP (20mmHg) and DBP below 10mmHg is considered as abnormal responses. The third sympathetic blood pressure reflex test involved sustained isotonic handgrip at about 30% of normal maximum strength using the dominant hand. Abnormal value was a drop in DBP below 15mmHg^{12,13}.

Data analysis

The data obtained were analysed using the SPSS computer software package version 12. Simple frequency distribution table was constructed. Mean was used as summarizing index, while the standard deviation was used as index of variation. Student t-test was used to assess for significant differences between mean of continuous variables. Chi square test was used to test for association between discrete variables. P value of 0.05 or less was taken as statistically significant.

Results

Age of the SCA patients ranged from 16 to 45 years with mean (SD) of 26.1 ± 5.1 years and age of control subjects ranged from 20 to 45 years with of 26.3 ± 5.1 years. Mean haemoglobin concentration of the SCA patients was 8.4 ± 2.4 g/dl, while their mean height and weight were 1.63 ± 0.1 m and 51.6 ± 11.1 kg, respectively. Controls had haemogram of 13.1 ± 0.9 g/dl, with mean height of 1.7 ± 0.1 m and weight of 62.4 ± 12.5 kg. Mean body mass index (SD) of control subjects and patients are 21.8 ± 4.2 kg/m² and 19.1 ± 3.2 kg/m², respectively. Baseline mean heart rate was higher in the SCA than controls [84 ± 12 beats/ minute Vs 76 ± 11 beats/minute ($P < 0.05$)]. Systolic and diastolic blood pressures were significantly higher in SCA patients (123 ± 11 mmHg and 79 ± 8 mmHg, respectively) than the control subjects (116 ± 14 mmHg and 68 ± 8 mmHg, respectively) with $P < 0.05$. This is shown in Table i. Three of the 6 cardiovascular autonomic reflex tests were used to assess the parasympathetic heart rate regulation. Significantly, greater proportions of SCA patients had abnormal values in 2 of the 3 tests. Eleven SCA compared to 2 controls had abnormal responses to deep breathing test ($P = 0.003$) while 15 SCA and 6 controls had impaired Valsalva ratio ($P = 0.01$). Abnormal values in heart rate responses from lying-to-standing position occurred in 8 SCA and 4 controls ($P = 0.2$). Although greater proportion of SCA patients compared to controls had abnormal responses to sympathetic blood pressure isotonic handgrip test the differences were insignificant ($P = 0.05$). Two SCA patients had drop in systolic blood pressure (SBP) below 20mmHg and only 1 patient had drop in diastolic blood pressure (DBP) below 10mmHg. None of the controls had drop in SBP and DBP below 20mmHg and 10mmHg respectively. This is further illustrated in table ii. Cardiovascular autonomic neuropathy was defined as the presence of 3 or more CAR tests, occurred 52.5% (21) SCA patients and 4.5% (11.5) controls with $P < 0.005$ (table iii).

Table i:
Baseline characteristics of SCA patients and controls

Characteristics	SCA Patients (N=40) Mean (SD)	Controls (N=44) Mean (SD)	P value
Age(years)	25±6	26±5	
Hb level(gm/dl)	8.4±2.4	13.1±0.9	0.001
Height(m)	1.6±0.1	1.7±0.1	0.002
Weight(kg)	51.6±11.1	62.4±12.5	0.0001
Body mass Index(BMI)	19.1±3.2	21.8±4.2	0.03
Heart rates (beats/min)	84±12	76±11	0.003
Systolic BP (mmHg)	123±11	116±14	0.04
Diastolic BP (mmHg)	79±8	68±11	0.001

Table ii:
Comparison of abnormal cardiovascular function tests in patients and controls

Autonomic function tests	SCA N=40(%)	Control N=44(%)	P value
Heart rate response to:			
Deep breathing (d*1.2)	11(27.5)	2(4.5)	0.003
Valsalva maneuver (d*1.4)	15(37.5)	6(13.6)	0.01
To standing 30:15 ratio(d*1.04)	8(20)	4(9.1)	0.2
Blood pressure response to:			
Systolic BP drop (d*20mmHg)	2(5)	0	-
Diastolic BP drop (d*10mmHg)	1(2.5)	0	-
To isometric handgrip (e*15mmHg)	7(17.5)	2(4.5)	0.05
Abnormal value (e*3tests)	21(53%)	4(9%)	0.00003

Discussion

Our result showed that CAN occur as part of the neurological complications seen in sickle cell anaemia. This is supported by the presence CAD in more SCA patients than controls with frequency of 52.5%. Functions of the parasympathetic arm of the cardiovascular autonomic nervous system appear to be severely impaired than those of the sympathetic. The proportion of SCA patients with CAD in this study is comparable to 58.3% documented by Romero *et al* from Brazil using heart rate variability measurement and clinical autonomic reflex tests⁹. Clinical implication and prognostic relevance of cardiovascular autonomic impairment has been established in some disease conditions like diabetes mellitus, hypertensive heart failure and alcoholic heart disease^{9,14,17}. Patients with CAN have been reported to have higher morbidity and mortality with reduction in quality of life^{1,12,18}. The pattern of autonomic dysfunction found in SCA patients in this study is similar to what had been documented in diabetes mellitus and hypertensive heart failure^{15,19,20}, while in chronic renal failure there is derangement in function of both arms of the cardiovascular autonomic nervous system¹⁶.

Our study was carried out during "steady state" when patients were crises free, which is to limit possible effects of acute sickle cell crises on our results. During this period subclinical vaso-occlusion has been reported²¹ which has been associated with various degrees of microvascular damage of different organ including nervous tissues²². The baseline data of the control subjects in comparison with

the homozygous sicklers revealed they were apparently healthier. The SCA patients had mean haemoglobin level of 8.4 ± 2.4 gm/dl, which is similar to 4 to 7 gm/dl reported as the baseline haemogram amongst Nigerians with SCA²³. This chronic anaemia is usually due to chronic haemolysis associated with recurrent malaria and sepsis that is common in SCA^{1,18}. Reports have it that whenever blood haemogram level falls below 8 gm/dl in SCA patients cardiac output could rise by as much as 50% above normal resting value²⁴. It was therefore not surprising that the mean heart rate in this group of SCA patients was significantly higher than controls. The finding of this study has important clinical relevance because the increase in resting heart rate in the background of chronic anaemia and possible autonomic impairment in favour of unopposed sympathetic activity will ultimately results in cardiac muscle hypertrophy and dilatation²⁵. The resulting higher demand for oxygen by the myocardium is likely to predispose to hypoxia-related arrhythmia²⁶. The long term consequence of this finding in SCA warrants further evaluation. We therefore recommend that further study on prognostic relevance of our findings need to be done and to relate autonomic impairment seen in SCA with other medical conditions in which CAN had been reported such as diabetes mellitus. In conclusion, this study has demonstrated that cardiovascular autonomic neuropathy is common in SCA patients, with relative preservation of the sympathetic limb of cardiovascular autonomic nervous system. These could be part of the several mechanisms responsible for high morbidity and mortality in SCA.

Part of the limitations of this study is the use of conventional clinical reflex tests to assess the cardiovascular autonomic functions and manual determination of ECG intervals. However, this conventional method has been established to be simple, reliable, and cheap^{12,13}. Also its results are reproducible and comparable to that of automated systems²⁷ which are not readily available in most centers in developing countries.

References

1. Serjeant GR. Sickle cell disease. *Lancet* 1997; 350: 725-30.
2. Adebayo RA., Balogun MO., Akinola NO., Akintomide AO. Cardiovascular changes in sickle cell anaemia. *Niger J Med* 2002; 11: 145-152.
3. Tsironi M., Aessopos A. The heart in sickle cell disease. *Acta Cardiol* 2005; 60: 589-98.
4. Covitz W., Espeland M., Gallagher D., Hellenbrand W., Leff S., et al. The heart in sickle cell anaemia. *Chest* 1995; 108: 1214-1219.
5. Kehinde MO., Temiye EO., Danesi MA. Neurological complications of sickle cell anaemia in Nigerian African- a case-control study. *J Natl Med Assoc* 2008; 100: 394-399.
6. Balkaran B., Char G., Morris JS., Serjeant GR. Stroke in a cohort study of patients with homozygous sickle cell disease. *J Pediatr* 1992; 120: 360-366.
7. Lester LA., Sodt PC., Hutcheon N., Arcilla R.A. Cardiac abnormalities in children with sickle cell anaemia. *Chest* 1990; 98: 1169-1174.
8. Cones P., Martin C., Barthetemy JC., Monchanin G., Atchou G., et al. Nocturnal autonomic nervous system activity impairment in sickle cell carriers. *Clin Physiol Func Imaging* 2006; 26: 87-91.
9. Romero Mestre JC., Hernandez A., Agrsmonte O., Hernanadedez P. Cardiovascular autonomic dysfunction in sickle cell anaemia: a possible risk factor for sudden death? *Clin Aut Res* 1997; 7: 121-125.
10. Jaja SI., Kehinde MO., Ogungbemi SI. Cardiac and autonomic response to change in posture or vitamin c supplementation in sickle cell anaemia subjects. *Pathophysiology* 2008; 15: 25-30.
11. Akinyanju OO. A profile of sickle cell disease in Nigerians. *Ann N Y Acad Sci* 2006; 565: 126-136.
12. Ewing DJ., Campbell IW., Clarke BF. Assessment of cardiovascular effects in diabetic autonomic neuropathy and prognostic implications. *Ann Intern Med* 1980; 92: 308-311.
13. Ravits J., Hallete M., Nilsson J., Polinsky R., Dambrosia J. Electrophysiological tests of autonomic function in patients with idiopathic autonomic failure syndromes. *Muscle Nerve* 1995; 19: 758-763.
14. Odusan O., Familoni OB., Raimi TH. Correlates of cardiac autonomic neuropathy in Nigerians with type2 diabetes mellitus. *Afr J Med Med Sci* 2008; 37: 315-320.
15. Casolo GC., Stroder P., Sulla A., Chelucci A., Freni A., et al. Heart rate variability and functional severity of congestive heart failure secondary to coronary artery disease. *Eur Heart J* 1995; 16: 360-367.
16. Sanya EO., Ogunnyi A. Cardiovascular autonomic neuropathy in non-diabetic Nigerian patients with chronic renal failure. *West Afr J Med* 2004; 23: 15-20.
17. Barter F., Tanner AR. Autonomic neuropathy in an alcoholic population. *Postgrad Med J* 1987; 746: 1033-1036.
18. Platt OS., Brambilla DJ., Rosse WF. Mortality in sickle cell disease: life expectancy and risk factors for early death. *N Engl J Med* 1994; 330: 1639-1644.
19. Haywood LJ. Cardiovascular function and dysfunction in sickle cell anaemia. *J Natl Med Assoc* 2009; 101: 24-30.
20. Saul JP., Arai Y., Berger RD., Lilly LS., Colucci WS., et al. Assessment of autonomic regulation in chronic congestive heart failure by heart rate spectral analysis. *Am J Cardiol* 1988; 61: 1292-1299.
21. Akinola NO., Stevens SME., Franklin IM., Nash GB., Stuart J. Subclinical ischemic episodes during the steady state of sickle cell. *J Clin Pathol* 1992; 45: 902-906.
22. Liesner RJ., Vanserberghe EA. Sudden death in sickle cell disease. *J R Soc Med* 1993; 86: 484-485.
23. Yetunde A., Anyaegbu CC. Profile of the Nigerian sickle cell anaemia patients above 30 years of age. *Cent Afr J Med* 2001; 47: 108-111.
24. Lindsay J., Meschel JC., Patterson R.H. Cardiovascular manifestations of sickle cell disease. *Arch Intern Med* 1974; 133: 643-651.
25. Lester LA., Sodt PC., Hutcheon N., Arcilla R.A. Cardiac abnormalities in children with sickle cell anaemia. *Chest* 1990; 98: 1169-1174.
26. Sangkatumvong S., Caotes TD., Khoo M.C. Abnormal autonomic responses to transient hypoxia in sickle cell anaemia. *Physiol Meas* 2008; 29: 655-668.
27. Howse M., Satsry S., Bell GM. Changes in corrected QT intervals and corrected QT dispersion during haemodialysis. *Postgrad Med J* 2002; 78: 273-275.