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Evaluation of Tp-e Interval and Tp-e/QTc Ratio among Patients with Steady State Sickle Cell Disease

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Abstract

Sickle cell disease (SCD) has been regarded as an inflammatory and pro-coagulatory disease with profound cardiovascular abnormalities including propensity for ventricular arrhythmogenesis. Tp-e and Tpe/QTc ratio however has been proposed as better indicators of arrythmogenesis and has been shown to be prolonged in many inflammatory conditions and correlate with levels of inflammatory markers. However, correlation between Tpe/QTc ratio and the level of highly sensitive C-reactive protein (hs-CRP) and plasminogen activator inhibitor (PAI) have not been reported in SCD. This study aims at evaluating Tp-e Interval and Tp-e/QTc ratio among steady state Sickle cell disease patients in relationship to the degree of anaemia, inflammatory and profibrotic markers. **Methodology:** A cross-sectional hospital-based study comprises 30 sickle cell anaemia patients in steady state with an equal number of controls having genotype HbAA and HbAS respectively. Clinical, laboratory and ECG parameters were obtained. **Results:** A total of 90 participants are with mean age 24.2 ± 5.6. The study showed that sickle cell disease patient had significantly lower level of PCV and higher level of PAI, platelet and total white cell count (p value < 0.05). C-reactive protein was also higher in them. 76.7% of HbSS patients had abnormal ECG. QTc and Tp-e were also prolonged in sickle cell disease patients compared with controls. An association was found between the level of PCV, PAI and prolonged Tp-e and QTc. **Conclusion:** Sickle cell disease patients have higher levels of inflammatory markers and abnormal ECG patterns are common in them. Moreover, the levels of these inflammatory markers correlate with Tp-e parameters.

Keywords

Electrocardiography, Arrhythmogenesis, Sickle Cell Anaemia, Inflammatory

1. Introduction

Sickle cell disease (SCD) is the most common single gene autosomal recessive Mendelian disease. Nigerians have the largest burden of the disorder anywhere in the world [1]. Cardiovascular abnormalities are often apparent in sickle cell disease, as in other chronic anaemias. Tissue oxygen extraction and cardiac output are increased. Moreover, the activated endothelium alongside the sickling process and the vaso-occlusion of the small blood vessels causes further strain to the cardiovascular system [2]. Electrocardiographic abnormalities are common in sickle cell anaemia. Several studies have reported varying electrocardiographic abnormalities in patients with sickle cell anaemia. Uzsoy and Ogunanobi found a prevalence of ECG abnormality as 78% and 96% respectively [3] [4] [5]. Winsor documented "non-specific" electrocardiographic abnormalities in the majority of 25 patients, while Adegoke observed other abnormalities including left ventricular hypertrophy, first degree atrioventricular block, nonspecific ST segment changes, prolonged QTc and right ventricular hypertrophy [6] [7].

There is increasing recognition of the prognostic implication of the spatial variations of QTc intervals and dispersion in normal individuals and patients with a variety of cardiac disease states [8]. Kolo observed that Mean corrected QT (QTc) in sickle cell patients was significantly higher than the mean of controls. Similarly, mean QT dispersion (QTcd) was higher in the former than in the latter; the study showed that cardiac autonomic neuropathy is a risk factor for abnormalities of QT parameters in SCA and both may be harbinger for cardiac death [9].

Recently, the interval from the peak to the end of T wave (T peak-Tend interval [Tp-e]) has been proposed for use in the prediction of malignant arrhythmia in SCD [10] [11] [12] [13]. Previous canine and rabbit left ventricular wedge models have indicated that the Tp-e interval in an electrogram was measured across the wedge correlates well with the transmural dispersion of cellular repolarization (TDR) [14]. Additionally, the Tp-e interval may serve as an index of total dispersion of repolarization (transmural, apico-basal, and global). Contemporary research has suggested that the Tp-e/QT ratio is a more accurate predictor of ventricular arrhythmias than the QT interval, corrected QT (QTc), or Tp-e [14]. Additionally, a higher Tp-e/QT ratio has been associated with arrhythmic events associated with many inflammatory and clinical conditions [12] such as in patients with slow coronary flow [15], ankylosing spondylosis [16], rheumatoid arthritis [17], obstructive sleep apnoea [18] and mitral valve prolapse [19] [20].

Considering documented evidence of higher prevalence of arrhythmias in SCD and the adverse outcome following it, early recognition of patients with

abnormalities of ventricular repolarization which is a harbinger of malignant arrhythmia is thus very important [21] [22]. Additionally, a higher Tp-e/QT ratio has been associated with arrhythmic events associated with many inflammatory and clinical conditions but this has not been documented in SCD, though it is an inflammatory and procoagulatory condition [12]. Moreover, the correlation between anaemia, inflammatory and profibrotic markers and Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio patterns has not been studied among patients with sickle cell anaemia in Nigeria.

2. Subjects, Materials and Methods

The study was carried out at the Haematology Department of LAUTECH Teaching Hospital, Ogbomosho, Oyo State. Subjects were sickle cell anaemia patients in steady state attending the outpatient unit of Haematology Department of LAUTECH Teaching Hospital, Ogbomoso, Oyo State. An equal number of age and sex matched normal subjects were selected from among medical and nursing students, hospital workers and members of the local community with genotype HbAA and HbAS served as controls. The study was a cross sectional hospital based study.

Only those who satisfied the selection criteria among consecutive subjects were involved in the study. Subjects with haemoglobin HbSS genotype, steady state was defined as absence of any crisis in the preceding four weeks with absence of any symptoms or signs attributable to acute illness. The control group comprised subjects with haemoglobin AA and AS genotype in two different groups, subjects with absence of congenital or acquired heart diseases, absence of pregnancy, and without any intercurrent illness.

We excluded subjects with diagnosis of acute or chronic illnesses such as malignancies, chronic kidney disease, chronic liver disease or infectious diseases, any kind of medical treatment as chemotherapy, radiotherapy or those on drugs known to prolong QTc such as halofantrin, risperidol, amiodarone, specific antibiotics and anti-histamines.

Approval was obtained from the Research and Ethical Review Committee of LAUTECH Teaching Hospital, Ogbomoso, Oyo State and from the University of Ilorin Ethical Review Committee. Informed consent was obtained from all participants in the study, all the cost of the study were borne by the investigators.

Patients with sickle cell anaemia were randomly selected by balloting at each haematology outpatient clinic visit over the study period. The controls consisted of age and gender matched students and members of staff of the hospital who had their haemoglobin electrophoresis done to confirm their genotype. Informed consent was obtained from all subjects, after which biodata and relevant history were obtained. General physical and systemic examinations were done. Blood samples were collected for full blood count, blood glucose, urea, creatinine, electrolytes, high sensitivity C-reactive protein (hs-CRP) and plasminogen activator inhibitor (PAI). ECG was done following the protocol below.

The initial assessment included a thorough medical history regarding cigarette smoking (or any other tobacco usage), alcohol consumption, family history of Hypertension, Diabetes Mellitus and/or Sudden Cardiac death and use of drugs.

Elevated waist circumference (WC) defined as ≥94 cm in men and ≥80 cm in women. Waist hip ratio (WHR) > 0.90 for men and 0.85 for women was also taken as abnormal. BMI ≥ 25 kg/m^2 across sexes was regarded abnormal. Hypertension, defined as systolic and/or diastolic BP ≥ 140/90 mmHg for adult.

A resting 12-lead Electrocardiography (ECG) using a Schiller portable ECG machine at a paper speed of 25 mm/sec and sensitivity of 10 mm was performed for both groups. ECG measurements were done with a ruler on the resting ECG tracings. P wave and QRS duration, RR, PR, QT and Tp-e intervals were manually measured. QT interval was defined as the time from the onset of the QRS to the point at which T wave returns to baseline. The QT interval was corrected (QTc) for the heart rate using the Bazett's formula. Prolonged QTc was defined as QTc ≥ 460 ms and 440 ms in females and males, respectively [23]. Tp-e interval was measured from the peak of T wave to the end of T wave. The end of the T wave was defined as the intersection of tangent to the down slope of T wave and isoelectric line as shown in **Figure 1**. If U wave was present, then T wave end was defined as the nadir between U and T wave. Measurement of Tp-e was performed in leads V2 and V5, the mean value of the measurement was used for the analysis [24].

Simple frequency distribution table was constructed. Mean was used as summary index, while the standard error of mean was used as an index of variation. Student *t*-test was used to assess difference between means of continuous variables. Chi square was used to test association between discrete variables. The groups were divided into 3: viz group A (HbAA genotype), group B (sickle cell trait), and group C (sickle cell disease). Analysis was correlated in all the groups. A multivariate analysis was performed in successive steps to estimate the association between Tp-e/QT Patterns (independent variable) and hs-CRP, PAI. A p value < 0.05 or 95% CI (CI95%) defined statistical significance. Data was analyzed by using the statistical package SPSS for Windows version 20.0 (IBM Company, Chicago, IL).

3. Results

A total of 90 young adults were recruited for the study, comprising 30 haemoglobin SS, AS and AA respectively. The overall male: female ratio was 1:1.2. Their age ranges from 17 to 46 years with a mean± SEM of 24.2 ± 5.6 years. The sociodemographic characteristics and anthropometric measurements of the cases and control are shown in **Table 1**. The HbSS group had significantly lower weight (53.2 ± 8.9 versus 64.1 ± 10.1 Kg), height (1.64 ± 0.08 vs 1.69 ± 0.07 m^2) and BMI (19.6 ± 2.6 vs 22.3 ± 2.9 Kg/m^2) compared to the control group (p < 0.001, 0.035 and <0.001 respectively).The HbSS group had lower mean diastolic blood pressure (58.2 ± 14.5 vs 75.1 ± 8.6) (p < 0.05) but higher pulse pressure (42.9 ± 12.3 vs 38.3 ± 10.6) than the HbAA group as shown in **Table 2**.

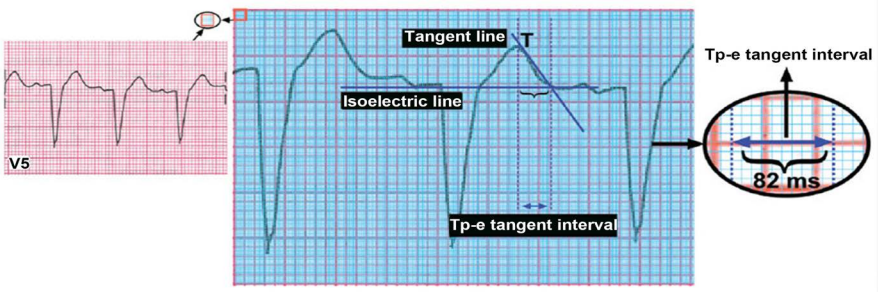

Figure 1. Measurement of the Tp-e interval using the tangent method. Adapted from Abdullah [24].

Table 1. Showing the sociodemographic characteristics and anthropometric measurements of the cases and control.

Baseline characteristics	HbAA	HbAS	HbSS	p-value
Sex M (%) F (%)	18 (43.9) 12 (24.5)	12 (29.3) 18 (36.7)	11 (26.8) 19 (38.8)	0.146
Age (years)	25.9 ± 5.5	21.6 ± 3.0	25.2 ± 6.8	0.005*
Weight (Kg)	64.1 ± 10.1	56.1 ± 8.1	53.2 ± 8.9	<0.001*
Height (m)	1.69 ± 0.07	1.64 ± 0.07	1.64 ± 0.08	0.035*
Waist circumference (cm)	80.2 ± 8.0	74.7 ± 6.3	76.8 ± 6.9	0.013*
Hip circumference (cm)	94.4 ± 7.7	87.9 ± 7.9	89.4 ± 7.4	0.005*
Waist hip ratio	0.85 ± 0.06	0.85 ± 0.05	0.86 ± 0.04	0.782
BMI (Kg/m^2)	22.3 ± 2.9	20.7 ± 2.6	19.6 ± 2.6	0.001*
Systolic BP (mmHg)	113.5 ± 10.8	111.4 ± 10.7	101.1 ± 19.9	0.003*
Diastolic BP (mmHg)	75.1 ± 8.6	70.6 ± 8.0	58.2 ± 14.5	<0.001*
Pulse pressure (mmHg)	38.3 ± 10.6	40.7 ± 8.3	42.9 ± 12.3	0.260

Key* = Statistically significant.

Table 2. Showing the haematological laboratory parameters of the cases and control.

Baseline characteristics	**HbAA**	**HbAS**	**HbSS**	**p-value**
PCV (%)	42.6 ± 4	40.5 ± 4	26.6 ± 6	<0.001*
Hbconc (mg/dl)	13.0 ± 1.2	12.7 ± 1.4	8.5 ± 1.4	<0.001*
RBC count	4.7 ± 0.6	4.8 ± 0.5	3.2 ± 0.6	<0.001*
Platelet count	227.3 ± 73	211.7 ± 67	331.5 ± 181	<0.001*
WBC count	4.0 ± 1.0	4.2 ± 1.2	6.7 ± 3.9	<0.001*
Glucose (mmol/L)	4.7 ± 1.2	3.9 ± 0.7	4.2 ± 1.6	0.030*
Hs-CRP	3.0 ± 0.8	4.1 ± 0.8	6.2 ± 1.3	0.106
High hs-CRP	4 (16%)	9 (36%)	12 (48%)	0.038*
PAI	13.5 ± 5.1	67.3 ± 15.3	92.7 ± 9.7	<0.001*
Urea (mmol/L)	2.6 ± 0.70	2.6 ± 0.20	2.6 ± 0.70	0.988
Creatinine (μmol/L)	135 ± 17.2	114 ± 15.2	100 ± 23.7	0.117

Key* = Statistically significant.

4. Laboratory Parameters of the Study Participants

SCD patients had significantly lower PCV (26.6 ± 6 vs 42.6 ± 4), haemoglobin concentration (8.5 ± 1.4 vs 13.0 ± 1.2) and red blood cell count (3.2 ± 0.6 vs 4.7 ± 0.6) with p values < 0.001 in all the three parameters. However, a significantly higher platelet count (331.5 ± 181 vs 227.3 ± 73) and white blood cell count (6.7 ± 3.9 vs 4.0 ± 1.0) was observed in the HbSS group compared with the HbAA as shown in Table 2. This study also shows that hs-CRP is higher in HbSS group than HbAS and HbAA groups respectively, though not significant (p = 0.106). However, categorizing hs-CRP into low, intermediate and high risk groups respectively using the WHO criteria of <1, 1 - 3 and >3 mg/dl respectively. Forty-eight percent (48%) of the HbSS group had high risk hs-CRP compared with 36% and 16% of the HbAS and HbAA groups respectively, p = 0.038.

5. Electrocardiographic Characteristics of the Study Participants

Table 3 shows the comparison of ECG indices between the cases and controls. The mean ECG-generated heart rate (HR), PR interval, corrected QT interval, Tp-e intervals and Tp-e/QTc ratio were higher among those with SCD than the controls. The average RV5 voltage and combined RV5 and SV1 voltages were also higher among the cases (p < 0.05), however, the mean QRS axis was lower (p < 0.05). ECG abnormalities (comparism between the HbAA and HbSS): left ventricular hypertrophy (53.3% vs. 33.3%), right atrial enlargement (6.7% vs. 0%) and T-wave inversion (10% vs. 3.3%) were more prevalent among cases than controls (p = 0.010, 0.129 and 0.585 respectively). In all 23 (76.7%) of the cases against 15 (50.0%) of the controls had at least one ECG abnormality (p = 0.02). Table 4 showed that haematocrit level had a weak negative correlation with Tp-e interval (r = –2.18), while PAI levels had a weak positive correlation with QTc (r = 0.258).

6. Discussion

SCD in its homozygous form has been linked with higher risk of ventricular arrhythmias and sudden death [9]. This study evaluates some of the risk factors

Table 3. Comparism of mean electrocardiographic indices between the study group.

ECG parameters	HbAA	HbAS	HbSS	p-value
Heart rate (beats/min)	67.6 ± 9.1	66.6 ± 9.3	73.5 ± 10.1	0.016*
QRS Axis (˚)	49.6 ± 18.4	53.5 ± 14.9	39.5 ± 22.4	0.017*
PR Interval(s)	0.19 ± 0.03	0.19 ± 0.04	0.20 ± 0.03	0.532
Tp-e Interval (ms)	80.0 ± 15	77.3 ± 14	83.0 ± 15	0.362
QTc	0.38 ± 0.03	0.37 ± 0.05	0.39 ± 0.08	0.764
Tp-e/QTc	0.211 ± 0.05	0.215 ± 0.05	0.230 ± 0.06	0.518
SV1 + RV5 (mm)	33.5 ± 12	26.8 ± 10	34.9 ± 11	0.018*

Key*= Statistically significant.

Table 4. Correlation between inflammatory markers and ECG parameters.

		QTC	Tp-e INTERVAL	Tp-e/QTc	Tp-e/QT
PCV	Pearson Correlation	−0.051	−0.218	−0.048	−0.017
	Significant	0.801	0.274	0.812	0.934
PLASMINOGEN ACTIVATOR INHIBITOR	Pearson Correlation	0.258	0.141	−0.212	−0.150
	Significant	0.176	0.467	0.271	0.438
C REACTIVE PROTEIN	Pearson Correlation	0.053	0.009	−0.001	0.044
	Significant	0.780	0.961	0.996	0.819

that have been linked with ventricular arrhythmias and sudden death. As described by Kato, progressive haemolysis-induced vasculopathy, one of the two major subphenotypes associated with clinical and laboratory manifestations of SCD, has been linked to endothelialdys function and the subsequent development of reticulocytosis, leg ulcers, priapism, stroke, elevated pulmonary arterial pressure and cardiac abnormalities in sickle cell disease [25].

6.1. Pattern of Laboratory Parameters in the Study Participants

The PCV, haemogblogin concentration and red cell counts were significantly lower among sickle cell disease subjects, similar to findings by Adegoke, this could be due to the ongoing haemolysis, nutritional deficiencies, frequent crises and repeated infections they are exposed to [7]. This study also showed higher values of white blood cell and platelet in the cases compared with control. This is similar to findings by other authors who observed relative thrombocytosis and leukocytosis [26] [27]. Thrombocytosis in steady state SCD has been attributed to the relative lack of splenic sequestration due to the auto-splenectomy seen in SCD patients. Moreover, SCD individuals have relatively higher levels of erythropoietin due to the anaemia in them; this erythropoietin has similar sequence homology with thrombopoietin which stimulate platelet production.

6.2. ECG Abnormalities in the Study Participants

The prevalence of any form of ECG abnormalities in our study was 76.7%. This is comparable to some reported rates among Nigerians with SCD. The significant finding of LVH is similar to many local reports [4] [5] [7]. Abnormal loading conditions associated with chronic anaemia lead to chamber dilatation and myocardial remodeling, which progress to ventricular dysfunction and hypertrophy, though genetic variations and polymorphism may also play important role [1] [2] [6] [28].

This study also demonstrated that the PR was prolonged and the mean Tp-e, QTc intervals and Tp-e/QTc ratio were longer in individuals with SCD compared with controls. These are not consistent with findings by other local authors [4] [29] [30]. However, the finding of this study was consistent with that of Odia who in an ECG study of 30 Nigerian sickle cell individuals aged 7 - 24 years

found no significant differences in QTc interval in patients compared controls [31].

The finding of increased Tp-e, Tp-e/QT ratio, and Tp-e/QTc ratio in SCD individuals is important. This result may contribute to pathophysiological mechanisms of increased prevalence of ventricular arrhythmias by indicating increased ventricular repolarization heterogeneity in SCD individuals. Some studies reported that increased dispersion of repolarization might predispose to ventricular arrhythmias [32] [33]. Moreover, few reports have confirmed the association between ventricular arrhythmogenesis and Tp-e prolongation [12] [34] [35] [36] [37] [38]. The duration of action potential is longer in the midmyocardial M cells compared to other myocardial cells. The earliest completion of repolarization occurs in the epicardial cells. The peak of T wave represents the end of the epicardial action potential, and the end of T wave represents the end of the mid-myocardial action potential. It has been reported that prolongation of Tp-e is associated with sudden cardiac death [39]. Thus, this result may explain the increased sudden cardiac death risk by showing that dispersion of ventricular repolarization is increased in SCD. Alterations in cardiac autonomic activity in SCD may be responsible for ventricular arrhythmias by increasing the heterogeneity of ventricular repolarization [9].

In this study, haematocrit level had a weak negative correlation with Tp-e interval, while plasminogen activator inhibitor had a weak positive correlation with QTc. Prolonged QTc and Tp-e interval are both established risk factors for sudden death. It is speculated that chronic anaemia, sub-acute cardiac ischaemia, cardiac autonomic neuropathy and microembolism may be associated with ventricular repolarization defects with ultimate prolongation of QTc [9].

7. Conclusion

This study showed that SCD patients have higher levels of inflammatory and profibrotic markers and abnormal ECG are common in them; moreover the Tp-e/QT ratio is higher in HbSS patients compared with controls. A weak correlation between the levels of these inflammatory and profibrotic markers and Tp-e/QT was observed.

8. Limitations

The statement below is not part of limitation, but under the authors responsibility. It was not included in the original manuscript sent.

9. Recommendation

Routine ECG should be done for patients with SCD for early detection of cardiovascular abnormalities to prevent development of dangerous malignant arrhythmias and sudden cardiac death. Optimal level of packed cell volume should be targeted in individuals with SCD, since lower levels increases risk of development of cardiovascular events.

Further studies with larger sample size may still be needed to correlate levels of inflammatory markers with development of arrhythmias, apart from repolarization abnormalities which is an index of arrhythmogenicity.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper. All the authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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