Electocardiographic findings in adult Nigerians with sickle cell anaemia

*Oguanobi NI[1], Onwubere BJC[1], Ike SO[1], Anisiuba BC[1], Ejim EC[1], Ibegbulam OG[2]

1-Department of Medicine,University of Nigeria Teaching Hospital Enugu, Nigeria
2-Department of Haematology, University of Nigeria Teaching Hospital Enugu, Nigeria

Abstract

Background: Cardiovascular system abnormalities are common causes of morbidity and mortality in sickle cell anaemia.
Objectives: The study aims at determining the pattern of electrocardiographic changes in adult Nigerian sickle cell anaemia patients.
Methods: A descriptive cross sectional study was done on sixty sickle cell anaemia patients seen at the adult sickle cell clinic of University of Nigeria Teaching Hospital (UNTH) Enugu, and sixty age and sex matched normal controls. All the subjects had clinical evaluation as well as electrocardiographic examination.
Results: The mean heart rate, P-wave duration, P-wave dispersion, PR interval, QRS duration, QRS dispersion, QTc interval and QTc dispersion were significantly higher in the patients than in the control group. Electrocardiographic abnormalities identified by this study were: left ventricular hypertrophy (75%; 1.7%), left atrial enlargement (40%; 0%), biventricular hypertrophy (11%; 0), ST-segment elevation (10%; 0%) and increased P-wave and QTc dispersions. ST segment elevation was found more in patients with moderate and severe anaemia (P= 0.02, Spearman correlation r= 0.342; P= 0.007),
Conclusion: Sickle cell anaemia is associated with significant electrocardiographic abnormalities. Further prospective studies are recommended to evaluate the prognostic significance of the electrocardiographic intervals dispersion on the long term disease outcome in sickle cell anaemia.

Key words: electrocardiographic findings, adult, sickle cell
African Health Sciences 2010; 10(3): 235 - 241

Introduction

Electrocardiographic abnormalities are common in sickle cell anaemia. Winsor and Burch[1] documented "non specific" electrocardiographic abnormalities in the majority of 25 patients. Uzsoy[2] found that 78% of 148 patients had an abnormal electrocardiogram. Abnormalities included left ventricular hypertrophy (18.4%), first degree atrioventricular block, and nonspecific ST – segment changes. Seven percent had electrocardiographic evidence of right ventricular hypertrophy. Of those with abnormal electrocardiogram, only 62% had a physical examination with abnormal results. It has been suggested that voltage criteria for ventricular hypertrophy be applied cautiously since there is evidence that higher voltages may occur as a normal racial variation in black population and the reduced skin fat and thin chest wall in patients with sickle cell disease may contribute to high recorded voltages[3,4,5].

***Correspondence author**:
Dr. Nelson I Oguanobi
Department of Medicine
University of Nigeria Teaching Hospital Enugu, Nigeria
Email: nelifyik@yahoo.com

Few data on electrocardiographic changes in sickle cell disease patients are found in African literature. Out of the thirty three (33) adult Nigerians with sickle cell anaemia studied by Adebiyi[6], seven (21.2%) had a prolonged QTc compared with normal control (none; 0%). The study also found significant T-wave inversion in the right precordial leads in sickle cell anaemia patients. It has been suggested that the T-wave abnormality might be an index of right ventricular ischaemia[7]. There is increasing recognition of the prognostic implication of the spatial variations of P- wave duration, QRS duration, and QTc intervals in normal individuals and patients with a variety of cardiac disease states[8,9,10]. However, these have not been well studied in sickle cell anaemia. The study aims at determining the pattern of electrocardiographic changes in steady state adult Nigerian sickle cell anaemia patients.

Methods

We conducted a descriptive cross sectional study on sixty sickle cell anaemia patients in steady state. These were drawn from patients attending the adult out patient sickle cell clinic of the University of Nigeria Teaching Hospital Enugu, Nigeria. An equal number

of age and sex matched normal subjects who were selected from among medical and nursing students, hospital workers and members of the local community served as controls. The inclusion criteria for the controls were: haemoglobin AA genotype, absence of congenital or acquired heart diseases, and absence of pregnancy and/intercurrent illness and haematocrit level e" 30%. Steady state is defined as absence of any crisis in the preceding four weeks, absence of any symptoms or signs attributable to acute illness. Informed consent was obtained from all the subjects.

All the participants were evaluated by electrocardiography. Resting 12-lead electrocardiography were performed on all subjects using cardioline Ar–600 model electrocardiography machine at a paper speed of 25mm/s and standardized at 0.1mv/mm. A single observer analyzed the electrocardiogram. Measurements of the heart rate, cardiac axis, PR- interval, QRS duration and QTc interval were done in the standard fashion[11]. Randomly selected electrocardiograms were cross checked for accuracy independently by two cardiologists. Electrocardiographic reference values for the black population proposed by Araoye were used as cut off values for duration of electrocardiographic deflections and intervals[11]. Electrocardiographic diagnosis of left atrial enlargement was based on the criteria described by Macruz and validated in the negro population by Araoye (widened P-wave e" 0.12mm, and or biphasic P-wave with the terminal force in V_1 e" 1mm, P-wave notching >40mm in lead II)[12,13]. Left ventricular hypertrophy on electrocardiogram was based on Sokolow and Lyon voltage criteria[14], While right ventricular hypertrophy was based on the criteria described by Allenstein et al; (dominant or tall R waves or Rs pattern in aVR, V_1 and V_2 with deep S wave in I, aVL, V_5, V_6)[15].

The dispersion of P-wave, QRS and QTc intervals were measured manually under magnifying glass by the same observer and were taken as the difference between the maximum and minimum values of each parameter on standard 12- lead electrocardiogram. The ST-segment was taken as the interval between the J point (or end of the QRS complex) and the beginning of the T wave (defined as the point of maximum abrupt deflation after the ST-segment)[11]. Elevation or depression of the ST-segment by 2mm or more from the isoelectric line was considered abnormal[7,11].

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). 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 e" 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%)[16]. Inter-class differences in clinical, electrocardiographic, 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. All statistical analyses were carried out using the Statistical Packages for Social Sciences (SPSS Inc. Chicago Illinois) software version 11.0 and EPi-Info version 3.4. Statistical tests with probability values less than 0.05 were considered statistically significant.

Variability of ECG measurements

Intra observer variability of manual ECG measurements was quantified by blinded and randomly sorted repeat measurements of 30 tracings a month after the original measurements were made. The mean absolute difference of measured parameters are shown in table 1. There was no statistically significant intra observer variability. The differences in electrocardiographic parameters among the groups cannot be explained by measurement variation.

Table 1: Intra observer variability of ECG measurements

ECG Parameters	Mean absolute difference (msec)	Standard Error of the diff. between means(SE diff)	T-test	P-value
P-wave duration	0.40	3.1083	0.1287	.875
P-wave dispersion	0.50	3.5399	0.1425	.868
PR-interval	0.40	6.4773	0.0618	.951
QRS-duration	0.06	5.9012	0.1017	.993
QRS- dispersion	0.50	4.0428	0.1237	.877
QTc-interval	1.3	5.5991	0.2322	.743
QTc- dispersion	1.0	5.2437	0.1907	.862

Results

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 statistically significant age and gender differences in patients and controls. The mean haematocrit values were 24.07±3.10 %; (range 20 – 31.3%) for the patients and 38.65±1.97%; (range 30 - 42%) for the controls. The mean haematocrit values was significantly lower in patients than controls (t= 30.589; P= 0.001).

Mean ECG indices

The mean heart rate, P-wave duration, P-wave dispersion, PR interval, QRS duration, QRS dispersion, QTc interval and QTc dispersion were significantly higher in the patients than in the control group (table 2).

Table 2: Comparison of electrocardiographic characteristics of patients and controls

Variables	Values (Mean SD)		T- Test	P- Value
	SCA	Controls		
Heart rate (beat/min)	80.61 (12.79)	68.98 (4.24)	6.327	< .001*
P-wave duration (msec)	128.0 (14.15)	90.30 (14.84)	14.189	< .001*
P-wave dispersion (msec)	65.7 (16.09)	34.7 (17.41)	9.014	< .001*
PR- interval(msec)	200.2 (28.79)	161.3 (27.13)	6.953	< .001*
QRS duration (msec)	85.0 (28.79)	81.5 (15.82)	2.111	.048*
QRS dispersion(msec)	53.0 (20.44)	33.3 (14.57)	5.774	< .001*
QTc- interval (msec)	415.7 (9.72)	393.5 (21.46)	7.300	< .001*
QTc- dispersion	100.0 (25.95)	47.8 (21.23)	44.792	< .001*

SCA- sickle cell anaemia *Statistically significant.

ECG abnormalities

Abnormal electrocardiographic findings in the patients and controls are compared in table 3. Electrocardiographic abnormalities were observed in 58 (96.7%) out of 60 patients studied; and in 2(3.2%) of the controls. Left ventricular hypertrophy based on Sokolow and Lyon voltage criteria[14], was found in 75% of the patients. Left atrial enlargement was found in 40% of the patients.

Table 3: Abnormal electrocardiographic findings in SCA patients and controls

Findings	Frequency (%)		χ - Square	P - Value
	SCA	Controls		
Left atrial enlargement	24 (40)	0 (0)	30.00	< .001*
LVH	45 (75)	1 (1.7)	68.25	< .001*
RVH	8 (13.3)	0 (0)	8.57	.003*
Biventricular Hypertrophy	7 (11.7)	0 (0)	7.43	.006*
1st degree AV Block	14 (23.3)	0 (0)	15.85	<. 001*
RBBB	5 (8.3)	0 (0)	5.22	.022*
ST-segment elevation	6(10)	0 (0)		0.02741*[a]
T-wave inversion in the right precordial leads.	8 (13.33)	1 (1.7)		0.03219*[a]
Prolonged QTc	37 (61.7)	0 (0)	53.49	<.001*
QTc dispersion > 90 msec	33 (55.0)	0(0)	45.52	< .001*

*Statistically significant (degree of freedom = 1), LVH- left ventricular hypertrophy, RVH- right ventricular hypertrophy, RBBB- right bundle branch block, SCA-Sickle cell anaemia, [a] =Fishers exact test.

Effect of haematocrit levels on electrocardiographic parameters

Electrocardiographic parameters and findings in the patients are compared among the haematocrit categories in tables 4 and 5. Significant difference was observed in the PR interval between with moderate anaemia compared with patients with severe anaemia (SE= 0.0101; P= 0.025) {Table 4} ST segment elevation was found more in patients with moderate and severe anaemia (^{2}=7.842; P= 0.02, Spearman correlation r= 0.342; P= 0.007),{ table 5}. The haematocrit value had no effect on other electrocardiographic parameters.

Table 4: Electrocardiographic parameters in sickle cell anaemia; effect of haematocrit levels

Parameters	Values: Mean(SD) Haematocrit levels			F- statistic	P- value
	Mild	Moderate	Severe		
Heart rate (beat/min.)	83.56(12.34)	77.65(12.85)	83.27(11.76)	1.391	0.297
P-wave duration (msec)	111.10(14.50)	136.50(17.31)	109.11(16.40)	0.228	0.797
P-wave dispersion (msec)	64.42(12.86)	64.04(17.10)	60.02(15.50)	0.245	0.784
PR interval (msec)	205.67(26.02)	190.00(24.32)	14.50(43.91)	3.402	0.040*
QRS duration (msec)	88.90(17.61)	88.00(20.15)	87.70(19.18)	0.095	0.910
QRS dispersion (msec)	48.94(17.64)	55.03(21.12)	47.33(20.51)	0.788	0.460
QTc Interval (msec)	448.93(28.04)	393.31(11.16)	454.56(30.50)	2.622	0.081
QTc dispersion (msec)	75.61(27.89)	105.00(23.21)	100.2218.55)	0.558	0.575

*Statistically significant.

Table 5: Comparison of abnormal ECG findings with relations to the haematocrit levels in SCA patients

Parameters	Frequency(%) Haematocrit levels			χ^2	P-value
	Mild	Moderate	Severe		
Prolonged QTc	5(55.56)	18(45.0)	9(81.81)	4.720	0.094
T-wave inversion	2(22.22)	2(5.00)	5(45.45)	1.662	0.436
L V H	7(77.78)	27(67.50)	9(81.81)	1.066	0.587
ST- Seg.elevation	0(0)	3(7.50)	3(27.27)	7.842	0.020*
LAE	5(55.56)	12(30.00)	6(54.55)	3.527	0.171
RVH	1(11.11)	7(17.50)	4(36.36)	2.442	0.295
RBBB	1(11.11)	5(12.50)	3(27.27)	1.602	0.449
LVH+RVH	0(0)	3(7.50)	3(27.27)	4.924	0.085
Ist degree AV block	3(33.33)	5(12.50)	3(27.37)	2.349	0.241

*Statistically significant (degree of freedom = 2), LAE = left atrial enlargement, χ^2= Chi- square.

Comparison of clinical, electrocardiographic and echocardiographic parameters in subsets of patients and controls with haematocrit values between 30 and 35 percent.

When a subset of the sickle cell anaemia patients (9 in number) with haematocrit levels ranging from 30 to 35.9% were compared with controls (11 in number) with similar haematocrit the patients were found to have significantly higher values than the controls in the measurement of pulse rate, P- wave duration, P- wave dispersion, PR interval, QRS duration, QRS dispersion, QTc interval, QTc dispersion, as shown in table 6.

Table 6: Comparison of clinical and ECG parameters in subsets of patients and controls with haematocrit level between 30 and 35.9%

Parameters	Values; Mean(SD)		T-Test	P-Value
	SCA; n =9	Controls; n = 11		
Age	26.11(3.59)	22.82(3.82)	1.972	0.064
Pulse rate	90.89(13.57)	72.19(5.33)	4.213	0.001*
P-wave duration	111.10(14.53)	89.14(16.45)	3.141	0.006*
P-wave dispersion	64.44(15.86)	36.43(10.35)	2.752	0.013*
PR interval	205.61(24.04)	165.52(9.34)	5.106	<0.001*
QRS duration	88.91(17.64)	73.66(18.04)	1.900	0.074
QRS dispersion	48.92(11.86)	31.87(9.28)	2.471	0.024*
QTc interval	448.96(28.04)	394.55(21.15)	4.945	<0.001*
QTc dispersion	75.64(27.89)	41.87(13.62)	3.194	0.007*

*Statistically significant.

Discussion

An over-view of electrocardiographic abnormalities

The prevalence of electrocardiographic abnormalities in sickle cell anaemia as shown in this study was 96.7%. This is relatively high compared to prevalence rates of 72.7% reported by Akinola[17] and 78% by Uzsoy[2]. These differences could be explained by the large number of electrocardiographic variables considered in this study.

Ventricular Hypertrophy

Left ventricular hypertrophy was the commonest abnormality found in 75% of the patients. This is similar to the findings of 70% and 63.8% respectively by Ng et al[18] and Akinola[17]. In contrast to the above, Aluko reported left ventricular hypertrophy in 48% of his study sample comprising mainly of children and adolescents[7]. This tends to suggest a possible increase in prevalence of left ventricular hypertrophy with age in sickle cell anaemia. Biventricular hypertrophy occurred in 11.7% in the present study and in 17.9% of patients in the study by Aluko[7].

QRS Duration, PR and QTc intervals and ST – T wave changes.

The PR interval was significantly prolonged in sickle cell anaemia patients compared to the controls (200.20±28.79 msec; 161.30±27.31 msec, respectively; P= 0.001). Prolongation of PR interval in the patients was still significant even when patients and controls with similar haematocrit were compared. Prolongation of PR interval > 0.21 seconds (first degree heart block) occurred in 23% of the patients. This is comparable to the occurrence in 29% of patients reported by Uzsoy[2], but differs significantly from occurrences in 50% and 9.1% respectively in studies by Klinefelter[19] and Akinola[17]. These differences could be as a result of different criteria of patients' selection used in the various studies.

This study demonstrated that the mean QTc interval was significantly longer in patients with sickle cell anaemia (415.7±9.72 msec) compared with normal controls (393.5+21.46) ;{ p = 0.001} The difference was also observed between patients and controls with mild anaemia. The frequency of QTc prolongation beyond the upper limit of normal (> 440 msec) was also higher in sickle cell patients (61.7%) than in the controls (0%). Adebayo et al[20], demonstrated significantly higher corrected QT interval in sickle cell patients compared with normal controls. These findings are similar to that of Bode–Thomas et al[21] in which 28% of sickle cell children studied had prolonged QTc. However, the finding of this study differs from that of Odia[22] who in an ECG study of 30 Nigerian sickle cell patients aged 7 – 24 years (mean 15.5± 4.25) found no significant differences in QTc interval in patients compared with 30 age and sex matched controls. Neither the actual mean QTc values nor the relative frequencies of QTc prolongation were however stated.

Prolongation of QTc interval implies abnormal repolarization from various causes[23,24]. It is also a known feature of myocardial ischaemia[25,26,27], which has been found in several patients with sickle cell anaemia especially during crisis[28,29,30].

Non specific ST segment elevation e" 2mm and T- wave inversion in the right precordial leads occurred in 10% and 13.33% of the patients

respectively in this study. Aluko[7] and Sergeant[31] found ST segment and T-wave changes in 9% and 5% respectively of adult steady state patients. Racial differences may explain the slightly higher values in this study when compared with the findings of Sergeant on Jamaican patients[31]. Although it has been suggested that the ST – T wave abnormality might be an index of myocardial ischaemia, no clear evidence of myocardial infarction was demonstrated by this study. In our study sample, isolated cases of ST segment and T-wave changes were observed and there were no significant Q-wave abnormality.

Dispersions of P-wave, QRS and QTc intervals

This study revealed significant prolongation of electrocardiographic intervals dispersion (P wave dispersion, QRS dispersion and QTc dispersion) in sickle cell anaemia patients. Increases in QTc dispersion and QRS dispersion have been shown to accompany myocardial ischaemia and various other disorders[32,33], and have been used to identify patients at risk for life – threatening arrhythmias after myocardial infarction[9,10,32].

A recent study in Turkey demonstrated significantly increased QTc dispersion in sickle cell patients compared with the controls subjects. Among sickle cell disease patients, those with pulmonary hypertension were found to have higher QTc dispersion than patients without pulmonary hypertension[34].

Conclusion

Sickle cell anaemia is associated with significant electrocardiographic abnormalities. Further prospective studies are recommended to evaluate the prognostic significance of the electrocardiographic intervals dispersion on the long term disease outcome in sickle cell anaemia.

Acknowledgement

The authors are grateful to Prof Augustine O. Obasohan of the University of Benin Teaching Hospital Benin City Nigeria for his very useful contributions. We also thank Mrs. Dora Okorogu of the Cardiac centre, University of Nigeria Teaching Hospital Ituku-Ozalla, Enugu Nigeria for offering technical support in electrocardiographic recording.

References

1. Winsor T, Burch GE. The electrocardiogram and cardiac state in active sickle cell disease. *Am Heart J*. 1945;29:685-696.
2. Uzsoy NK. Cardiovascular findings in patients with sickle cell anaemia. *Am J Cardiology*. 1964; 13:320-328.
3. Balfour IC, Covitz W, Davis H, Rao PS, Strong WB, Alpert BS. Cardiac size and function in children with sickle cell anaemia. *Am. Heart J*. 1984; 108:345-350.
4. Araoye MA. Left ventricular hypertrophy by electrocardiography: A code system applicable to Negroes. Nig Postgrad Med J 1996; 3:92-97.
5. Araoye MA. LVH. By ECG; Letter to the Editor. *Nig Postgrad J* 1999;6:189.
6. Adebiyi AA. Left ventricular systolic function of Nigerians with sickle cell anaemia attending the University College Hospital Ibadan. WACP Dissertation. West Africa Postgraduate Medical College. October 1996.
7. Aluko OA. The heart in sickle cell disease. FMCP Dissertation. National Postgraduate Medical College of Nigeria. 1985.
8. Dilavaris PE, Gialafos JE. P-wave dispersion: a novel predictor of paroxysmal atrial fibrillation. *Ann Noninvasive Electrocardiol* 2001; 6:159-165.
9. Anastasiou-Nana MI, Nanas JN, Karagounis L A, et al. Relation of Dispersion of QRS and QT in patients with advanced congestive heart failure to cardiac and sudden death mortality. *Am J Cardiol* 2000; 85: 1212-1217.
10. Darbar D, Luck J, Davidson N, et al. Sensitivity and specificity of QTc dispersion for identification of risk of cardiac death in patients with peripheral vascular disease. *BMJ* 1996; 312: 874- 879.
11. Araoye MA. Left ventricular hypertrophy by electrocardiography: A code system applicable to Negroes. *Nig Postgrad Med J* 1996; 3:92-97.
12. Macruz R, Perloff JK, Case RB. A method for the electocardiographic recognition of atrial enlargement. *Circulation*. 1958; 17: 882-889.
13. Araoye MA, Oladigo OG, Omotoso ABO. Appraisal of the electrocardiographic signs of left a trial enlargement. *Nig. Postgrad. Med. J*. 1999;6: 161 -166.
14. Sokolow M, Lyon TP. The ventricular complex in left ventricular hypertrophy as obtained by unipolar leads. *Am. Heart J*. 1949;37: 161-186.

15. Allenstein BJ, Mori H. Evaluation of electrocardiographic diagnosis of ventricular hypertrophy based on autopsy comparison. *Circulation* 1960; 21:404-412.
16. DeMaeyer EM. Preventing and controlling iron deficiency anaemia through primary health care. Geneva, World Health Organization 1989.
17. Akinola NO. Cardiovascular status of Nigerian individuals with sickle cell anaemia. FMCP Dissertation. National Postgraduate Medical College of Nigeria. 1994.
18. Ng M.L., Leibman J., Anslovar J., Cross S., Cardiovascular findings in children with sickle cell anaemia. *Dis. Chest.*1967; 52:788-99.
19. Klinefelter HF. The hearts in sickle cell anaemia. *Am J Med Sci.* 1942; 203: 34-51.
20. Adebayo RA, Balogun MO, Akinola NO, Akintomide NO. The clinical, electrocardiographic and self-paced walking exercise features of Nigerians with sickle cell anaemia at OAUTHC, Ile-Ife. Nig. J. Med. 2002; 11:170-176.
21. Bode Thomas F, Ogunkunle OO, Omotoso AB. The QT Interval in Nigerian Children with sickle cell anaemia, *Tropical cardiology*. 2003; 29(113):9-12.
22. Odia OJ. Electrocardiographic observations in patients with sickle cell diseases. *Tropical cardiology* 1990; 16:135-138.
23. Lo SS, John Sutlon M, Leshe RD. Information on type 1 diabetes mellitus and QT interval from identical twins. *Am J Cardiol* 1993; 72:305-309.
24. Moss AJ. Prolonged QT interval syndromes. *JAMA* 1986; 256: 2985-2987.
25. Puddu PE, Bourassa MG. Prediction of sudden death from QTc interval prolongation in patients with ischaemic heart disease. *J electrophysiol* 1986; 19:203-212.
26. Kraemer B, Brill M, Bruehn A et al. Relationship between the degree of coronary artery disease and left ventricular function and the duration QT interval in ECG. *Eur Heart J* 1986;7:14-24.
27. Schwartz P, Wolf S. QT interval prolongation as predictor of sudden death in patients with myocardial infarction. *Circulation* 1978; 57:1074-1077.
28. Norris S, Johnson CS, Haywood LJ. Sickle cell anaemia: does myocardial ischaemia occur during crisis? *J Natl Med Assoc* 1991;83: 209-213.
29. Martin CR, Cobb C, Tatter D , et al. Acute myocardial infarction in sickle cell anaemia. *Arch Intern Med* 1983;143: 830 -831.
30. MC Cormick WF. Massive nonatherosclerotic myocardial infarction in sickle cell anaemia. *Am J Forensic Med Pathol* 1988; 9:151-154.
31. Serjeant GR. Sickle cell disease. Second edition. Oxford, New York. 1992; 129 – 138.
32. Glacy J M, Garratt CJ, Woods KL, de Bono DP. QT dispersion and mortality after myocardial infarction. *Lancet* 1995; 345:945 – 948.
33. Day CP, Mc Comb JM, Campbell RW. QT dispersion: an indication of arrhythmia risk in patients with long QT intervals. *Br Heart J* 1990; 63:342 – 344.
34. Akgul F, Seyeli E, Melek I, Duman T, Seyclaliyeva T, Gali E, Yalcin F. Increase QT dispersion in sickle cell disease: Effect of pulmonary hypertension. *Acta Haematological* 2007; 118(1):1 – 6.