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The Effect of Iron Replacement Therapy on Electrocardiographic Consequences in Pediatric Patients

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Abstract

Background

Sudden cardiac death is an important problem, because the patients have no opportunity to receive medical service. Recently some electrocardiogram (ECG) parameters are used for predicting arrhythmias, including P wave duration for predicting atrial arrhythmias and corrected QT and T wave peak to end interval (Tp-e), for predicting ventricular arrhythmias. Iron deficiency is the most prevalent nutrient disorder worldwide in which iron loads in different tissues including myocardium are decreased. We aimed to investigate the relationship between iron deficiency and arrhythmogenic ECG parameters. Then we compared electrocardiographic parameters of iron deficient patients before and after iron replacement therapy.

Materials and Methods

In the first phase of study, ECG and blood samples were taken from 9-18 years old healthy adolescents for CBC and ferritin tests. They were divided into three groups according to serum ferritin: group 1 (ferritin below 15), group 2 (ferritin 15-30), and group 3 (ferritin above 30) ng/ml. In phase two, group 1 were given standard iron replacement therapy. We compared ECG parameters in three groups and then in group 1 before and after treatment.

Results

The number of individuals in three groups was 120 (group 1= 25, group 2= 26 and group 3= 69). The results showed that all parameters were significantly higher in group one and the lowest in group three. Also, there was a significant decrease in these parameters after treatment in group one ($P<0.05$).

Conclusion

Based on the results, Iron deficiency through decreased myocardial iron load can prolong ECG parameters and elevate risk of arrhythmia. Also, iron replacement therapy can reduce this risk.

Key Words: Adolescents, Iron deficiency, Arrhythmia; Ferritin, P wave dispersion.

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1- INTRODUCTION

Iron deficiency is the most common nutritional disorder worldwide with an involvement of about 30% of universal population especially in developing countries (1). Ferritin, mostly secreted by macrophages and hepatocytes, has relatively low amounts of iron but serum level of ferritin is correlated with total body iron reservoir (2). Measurement of serum ferritin level is the most proper laboratory test for estimating body iron load (3). In heart, iron is preferred for production of myoglobin and cytochromes. Rat fetus was exposed to chronic hypoxia and maternal iron deficiency caused by reduced iron concentration in myocardium but all proteins were not affected similarly (4). On the other hand, there are some parameters in surface electrocardiogram which can be used for predicting atrial and ventricular arrhythmias. Prolongation of P ware duration and its dispersion in different leads can predict atrial fibrillation and also corrected QT interval (QTc), T wave peak to end interval (Tp-e), and Tp-e/QTc ratio (called arrhythmogenic index) can predict ventricular arrhythmia (5). In normal heart subendocardium depolarizes before subepicardium but subepicardium repolarizes before subendocardium demonstrating ST segment and T wave. In children, repolarization potentials appear about ten milliseconds before end of ventricular depolarization (6). The peak of T wave is coincident with end of epicardial repolarization whereas the end of T wave indicates end of M cells repolarization, thus Tp-e interval in each lead is proposed as transmural repolarization index. Many drugs affect QTc which is the most common cause of excluding them (7). Few surveys are already conducted on the relationship between body iron loads and prolongation of arrhythmogenic ECG parameters. It was our goal to evaluate this relationship between iron deficiency and arrhythmogenic ECG parameters and the effect of iron replacement therapy on these parameters.

2- MATERIALS AND METHODS

2-1. Study design and population

At first we visited all 9-18 years old adolescents referred to Vali-e-Asr hospital, Birjand city, Iran, during November 2018 to January 2019 and according to parental consent and inclusion and exclusion criteria, 120 people were included in our study. The aim of number of iron deficient patients was 19 people according to average estimation formula and the result of previous studies (21). We increased this number to 25 people for more accuracy. Then, the aim of study was explained to the participants and their parents. Afterward detailed history was taken and general and cardiac physical exam was performed. Height and weight were recorded and a twelve lead standard ECG was taken. Lastly, 4 ml of venous blood was sampled and sent to referral laboratory for CBC and ferritin tests.

2-2. Measuring tools

- Progetti S.r.l.: EPG 6 view INT Italy for ECG recording by a trained pediatric resident.
- A tape with the margin of error of 0.5 cm and a German scale (Seka) with the margin error of 50 gr which was calibrated by means of a control scale every day for measuring height and weight by a trained pediatric resident.

2-3. Laboratory measurements

Sysmex Kx 21N Japan for CBC and Cobas e411 analyzer/2008/Japan and Germany Rosh kits by Electrochemiluminescence (ECL) method for ferritin tests.

2-4. Intervention

Patients who have serum ferritin level below 15 ng/ml as iron deficient patients

(1) were informed about iron deficiency and importance of treatment. They were treated by supplemental iron tablets with generic name of ferrous sulfate and trade name of Feriron made by Daroopakhsh, Batch number: 796 consisting of 50 mg elemental iron given as 5 mg elemental iron per kilogram (max dose 150 mg) daily for three months. Then the patients were visited again and after taking history and physical exam, standard ECG was done by the same apparatus and CBC and ferritin tests were performed by the same methods and instruments.

2-5. Ethical considerations

The research issue was approved by Ethical Committee of Birjand University of Medical Sciences with ID-code: Ir.bums.REC.1397.037 according to Ethical Guidelines of the 1975 Declaration of Helsinki and was recorded in IRCT Corporation with number: IRCT2019011404235TN1. An informed consent was used for participants (they were under 18 years old) and their parents.

2-6. Inclusion criteria

Inclusion criteria were absence of any acute inflammatory disease during past month, or any chronic disease, congenital or structural heart disease and any drug consumption during last month.

2-7. Exclusion criteria

Only one patient was excluded from second phase of the study because of low serum ferritin after therapy.

2-8. Data analysis

A questionnaire was composed including personal information, age, sex, height, weight, vital signs, and data of electrocardiogram and results of lab tests. Distances of ECG parameters were measured by a pediatric cardiologist in proportion to milliseconds blindly by MG13100 Illuminated scale-magnifier. Buzzet formula was used for calculating QTc. Lead II is proffered for measuring QTc because it consists of Q wave and precordial leads V_5 or V_4 are proper for measuring Tp-e (8, 9). We used lead II for calculating P wave interval and QTc and V_5 for Tp-e and in a few cases that V_5 was impaired, V4.ECGs were used; cases which had more than two obscure leads were discarded and replaced with new strips. Individuals were classified to three groups according to their serum ferritin; **Group 1**: ferritin less than 15 ng/ml as iron deficient. **Group 2**: ferritin 15-30 ng/ml as borderline iron load, and **Group 3**: ferritin above 30 ng/ml as iron sufficient. Data were analyzed using SPSS software version 22.0, descriptive information was presented and the results were analyzed by statistical tests in the error level of $\propto = 0.05$. In the first phase of the study the normal distribution of all parameters was checked by Kolmogrov-Smirnov test. The results showed that only Tp-e variable has normal distribution. Thus ANOVA test was performed for comparison of mean of this variable in three groups. Other variables were tested by Kruskal-Wallis H and Mann-Whitney. In second phase of the study Wilcoxon test was used.

3- RESULTS

The population of the study was 120 healthy adolescents aged 9 to 18 year-old living in Birjand city, Iran. All of them were students. According to ferritin level, there were 25 patients in group one, 26 people in group two and 69 in group three. **Tables 1 and 2** show that three groups were homogenous according to sex and age and there was no meaningful difference. **Table.3** indicates that all of arrhythmogenic parameters of ECG were longest in group one (ferritin<15 ng/ml), and shortest in group three (ferritin<15 ng/ml), and these differences were significant statistically (P<0.001).

Table-1: Distribution of participants in three groups, according to gender (n=120).

Variables	Group 1 Ferritin < -15 ng/ml	Group 2 Ferritin 15-30 ng/ml	Group 3 Ferritin > 30 ng/ml	Result of statistical tests
Gender	Number (percent)	Number (percent)	Number (percent)	
Female	16 (17.6)	19 (20.9)	56 (61.5)	Chi-squre=3.09
Male	9 (31.0)	7 (24.1)	13 (44.8)	
Total	25 (20.8)	26 (21.7)	69 (57.5)	P=0.21

Table-2: Mean age in three groups of participants (n=120).

Ferritin, ng/ml	Mean ± SD	Number	F	P-value
< 15	12.79±2.74	25	0.30	0.74
15-30	12.69±2.14	26		
> 30	12.39±2.56	69		

SD: Standard deviation.

Table-3: Comparison of ECG parameters in three groups of participants (n=120).

ECG Parameters	Ferritin < 15 ng/ml		Ferritin 15-30 ng/ml		Ferritin > 30 ng/ml		P-value
	Med $(Q_1 - Q_3)$	Mean ± SD	Med $(Q_1 - Q_3)$	Mean ± SD	Med $(Q_1 - Q_3)$	Mean ± SD	
P wave interval	106.24±4.33	108 (104-108)	96.15±2.39	96 (96-96)	76-81±10.39	50 (68-84)	$\mathcal{K}^2 = 92.83$ $P < 0.001$
P wave dispersion	41.76±6.54	44 (40-48)	25.31±5.96	28 (20-32)	17.80±5.20	16 (12-20)	$\mathcal{K}^2 = 92.83$ $P < 0.001$
QTc	462.40±6.70	464 (455-467)	435.74±8.18	433 (428 – 441)	405.96±2.54	408 (397-418)	$\mathcal{K}^2 = 94.12$ $P < 0.001$
QTc dispersion	66.08±18.28	67 (53-73)	38.69±10.91	37.50 (30-47)	29.39±12.54	27 (22-35)	$\mathcal{K}^2 = 56.42$ $P < 0.001$
Tp-e	103.04±7.94	----	91.31±4.79	----	76.12±8.76	----	$F = 118.14$ $P < 0.001$
Tp-e dispersion	38.56±8.07	40 (36-44)	23.08±4.71	24 (20-28)	17.39±5.17	16 (12-20)	$\mathcal{K}^2 = 61.95$ $P < 0.001$
Tp-e/QTc Ratio	0.22±0.016	----	0.21±0.011	----	0.18±0.015	----	$F = 62.11$ $P < 0.001$

QTc: Corrected QT interval; QTc dispersion: Difference of longest and shortest QTc; Tp-e: T wave peak to end distance; Tp-e dispersion: Difference of longest and shortest Tp-e.

Regression model was used to study the relation between ferritin and each of the ECG parameters individually, which is manifested as top seven rows of **Table.4** and **Figures 1-7** (*Plase see tha table.4 and figures 1-7 in the end of paper*). The results show that there is a reverse linear relationship between ferritin and each of the ECG parameters whose P-value is less than 0.001 in all cases, that means

whenever ferritin is increased these parameters will be shortened and ferritin can predict the distance of them. In the bottom seven rows of **Table.4** the relation between hemoglobin and each of the ECG parameters is shown by regression model. The results show that there is also a relation between hemoglobin and each ECG parameter, and hemoglobin can predict them but P-value is more than 0.001 which demonstrates that the relationship between ferritin and ECG parameters is stronger than between hemoglobin and these parameters. The concentration of hemoglobin was 13.20$\pm$ 1.68 gr/dl in group one, 14.1$\pm$1.4 in group two and 14.16$\pm$1.59 in group three (F=3/61, P=0.030). It was a little lower in group one than group three (P=0.03); but there was no significant difference between groups two and three (P=0.99). During the second phase of the study, iron deficient patients (group one) were treated by supplemental iron tablets. In 24 of them ferritin elevated to a normal range, but in one patient ferritin was decreased because of new onset abnormal uterine bleeding. She was referred to gynecologist and admitted in hospital and was excluded from study. **Table.5** compares ECG parameters before and after treatment and shows that there is a significant reduction after treatment.

Table-5: Comparison of ECG parameters before and after treatment in patients with ferritin less than 15 ng/ml.

ECG Parameter	Before treatment		After treatment		Result of statistical of tests	
	Mean ± SD	Med ($Q_1 - Q_3$)	Mean ± SD	Med ($Q_1 - Q_3$)	Z	P-value
P wave interval	106.24±4.33	108 (104-108)	58.67±7.32	56 (52-60)	-4.30	<0.001
P wave dispersion	41.76±6.54	44 (40-48)	13.17±4.17	12 (10-16)	-4.31	<0.001
QTc	462.40±6.70	464 (455-467)	377.54±15.3	380 (365-387)	-4.29	<0.001
QTc dispersion	66.08±18.28	67 (53-73)	24.42±7.35	26 (17-29)	-4.29	<0.001
Tp-e	103.04±7.94	104 (100-108)	59.33±7.52	58 (52-64)	-4.30	<0.001
Tp-e dispersion	38.56±8.07	40 (36-44)	12.67±3.67	12 (12-16)	-4.22	<0.001
Tp-e/QTc Ratio	0.22±0.02	0.22 (0.22-0.23)	0.16±0.01	0.15 (0.15-0.17)	-4.29	<0.001

SD: Standard deviation. QTc: Corrected QT interval, QTc dispersion: Difference of longest and shortest QTc, Tp-e:T wave peak to end distance, Tp-e dispersion: Difference of longest and shortest Tp-e.

4- DISCUSSION

We compared modern electrocardiographic repolarization parameters of iron deficient adolescents with borderline and iron sufficient individuals and results showed that iron deficiency can prolong them. These parameters of sudden death are very important because a longer P wave interval and increasing of its dispersion among twelve leads can predict atrial fibrillation in future. Also, increased QTc, QTc dispersion, Tp-e interval, Tp-e dispersion and Tp-e to QTc ratio can predict ventricular arrhythmias especially torsade de pointes (10,11). These parameters may be increased in children in proportion to age but during adolescence they remain constant and sex has no effect on them (12). In children with positive tilt test for syncope, these parameters are longer (13). Ghandi et al. showed that iron overload

defined by elevated ferritin in thalassemic children can prolong QTc and QTc dispersion (14). Thus both iron overload and iron deficiency can prolong arrhythmogenic markers. Some clinical conditions such as subclinical hypothyroidism, celiac disease, obesity, rheumatic carditis, ventricular septal defect and mitral value prolapse may prolong parameters and increase risk of arrhythmia (15-20). In Simsek et al.'s survey iron deficient patients had a longer P wave interval (91.1±18.0 vs. 85.8±6.71 msec) (P=0.054), and P wave dispersion (48.1±7.7 vs. 40.9±5.6 msec) compared with control group (21).

Our study also showed that P wave interval and dispersion was longest in group one (ferritin<15 ng/ml), and shortest in group three (ferritin<15 ng/ml), which confirms Simsek et al.'s study (21). Karadeniz et al., divided children with no structural heart disease to three groups according to their serum ferritin: < 15, 15-25 and > 25 ng/ml. P wave duration, QT and Tp-e intervals and dispersion in P wave, QT, QTc and Tp-e were significantly higher in children with ferritin < 15 and there was a negative correlation between ferritin level and QT, QTc, QTc dispersion and Tp-e dispersion (22), that was very similar to our research but they do not follow up and treat patients.

We studied 120 adolescents with serum ferritin: 2.4-144.9 ng/ml for their arrhythmogenic ECG parameters and results showed that P wave duration and dispersion, QTc, QTc dispersion, Tp-e, Tp-e dispersion and Tp-e/QTc ratio were highest in iron deficient group and lowest in iron sufficient group. In addition, there was a negative linear relation between ferritin and the individual parameters. Thus deficit in body iron loads probably due to reduction in myocardial iron load changes the electrophysiological properties of heart and induces heterogeneity in repolarization that shows itself by increasing arrhythmogenic parameters. Although hemoglobin has a negative relation with the parameters too, this relation was weaker and shows that iron deficiency prior to anemia can effect on the parameters so that in groups two and three with no significant difference in hemoglobin, ferritin reduction was related with increase in parameters. We treated iron deficient patients and showed that filling of iron storage can shorten ECG arrhythmogenpc parameters. It means that arrhythmogenic change of ECG is reversible by iron supplement therapy probably due to myocardial iron load returning to normal. Iron deficiency has been cynosure from a long time ago because of its important complications such as anemia. We manifest one other aspect of importance of diagnosis, prophylaxis and treatment of iron deficiency. Reducibility of arrhythmogenicity was not studied before. We hope future studies clear mechanisms of iron deficiency effect on electrocardiographic parameters.

4-1. Study Limitations

1) Participants in groups 2 (ferritin between 15 and 30 ng/ml) and group 3 (ferritin>30 ng/ml) were not followed up and their ECG parameters were not assessed during the time.

2) Iron deficient individuals were not followed long term for reversibility of iron deficiency and ECG parameters.

3) There was no control group for iron replacement therapy.

5- AUTHORS' CONTRIBUTION

Study concept and design, Acquisition of data, Analysis and interpretation of data, Drafting of the manuscript, Statistical analysis: V.Sh; Critical revision,

Administrative, technical and material support: F.S.A.; Study supervision: F.A.

5- CONCLUSIONS

Based on the results, deficiency in total body iron loads can significantly change some parameters of electrocardiogram that are important in anticipation of arrhythmia. On the other hand filling of iron stores can return arrhythmogenic changes of ECG to normal. Thus screening prevention and treatment of iron deficiency are protective on cardiac health in addition to other well-known benefits.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENTS

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Table-4: Changes of ECG parameters in relation to ferritin and hemoglobin separately.

Parameters	Regression						Coefficients						
	R	R square	Adjusted square	Standard error of estimate	F	P-value	Model predict constant	Unstandardized coefficients			Standardized coefficients	T	P-value
								α	β	Standard error			
P wave interval	0.948	0.898	0.898	4.77	1044.20	<0.001	Ferritin	107.946	-0.514	0.016	-0.948	-32.314	<0.001
P wave dispersion	0.74	0.549	0.545	7.399	143.52	<0.001	Ferritin	36.36	-0.295	0.025	-0.74	-11.98	<0.001
QTc	0.923	0.852	0.851	10.18	679.22	<0.001	Ferritin	459.96	-0.884	0.034	-0.92	-26.06	<0.001
QTc dispersion	0.587	0.345	0.339	22.37	62.04	<0.001	Ferritin	56.100	-0.421	0.053	-0.58	-7.88	<0.001
Tp-e	0.90	0.817	0.816	5.84	527.82	<0.001	Ferritin	103.194	-0.447	0.019	-0.90	-22.97	<0.001
Tp-e dispersion	0.68	0.46	0.46	7.39	104.18	<0.001	Ferritin	33.212	-0.251	0.025	-0.68	-10.20	<0.001
Tp-e/QTc Ratio	0.855	0.731	0.729	0.01	321.289	<0.001	Ferritin	0.23	-0.001	<0.001	-0.85	-17.92	<0.001
P wave interval	0.262	0.69	0.061	1.55	8.54	0.004	Hemoglobin	16.471	-0.029	0.010	-0.26	-2.92	0.004
P wave dispersion	0.229	0.052	0.044	10.66	6.42	0.013	Hemoglobin	46.120	-1.555	0.614	-0.23	-2.53	0.013
QTc	0.296	0.088	0.08	25.01	11.15	0.001	Hemoglobin	491.50	-4.808	1.44	-0.29	-3.34	0.001
QTc dispersion	0.287	0.08	0.075	19.01	10.41	0.002	Hemoglobin	88.473	-3.53	1.09	-0.28	-3.22	0.002
Tp-e	0.272	0.074	0.066	12.94	9.25	0.003	Hemoglobin	116.88	-2.266	0.745	-0.27	-3.04	0.003
Tp-e dispersion	0.24	0.058	0.05	9.70	7.12	0.009	Hemoglobin	43.78	-1.490	0.56	-0.24	-2.66	0.009
Tp-e/QTc Ratio	0.24	0.06	0.05	0.02	7.39	0.008	Hemoglobin	0.24	-0.003	0.001	-0.24	-2.72	0.008

QTc: Corrected QT interval; QTc dispersion: Difference of longest and shortest QTc; Tp-e: T wave peak to end distance; Tp-e dispersion: Difference of longest and shortest Tp-e.

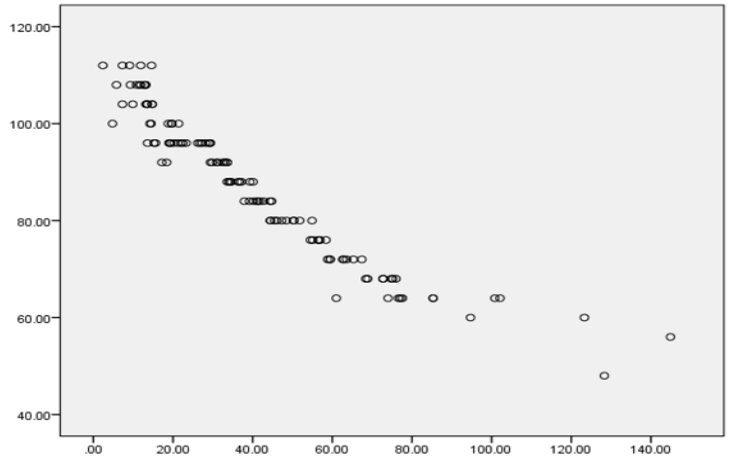

Fig.1: P wave interval changes in relation to ferritin

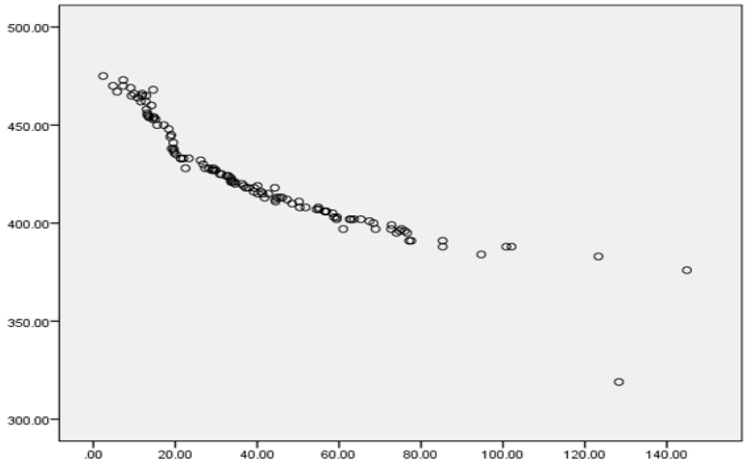

Fig.3: QTc changes in relation to ferritin

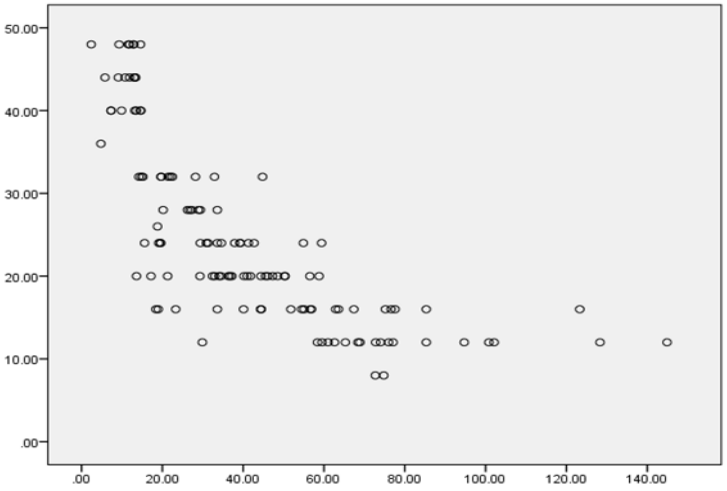

Fig.2: P wave dispersion changes in relation to ferritin

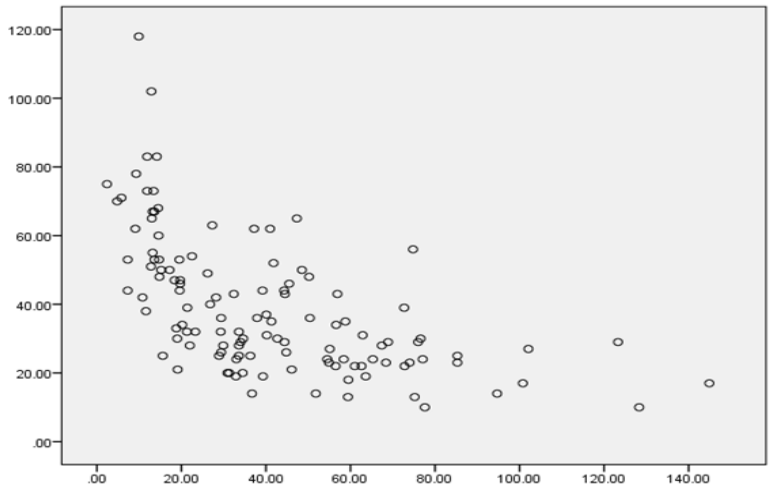

Fig. 4: QTc Dispersion changes in relation to ferritine

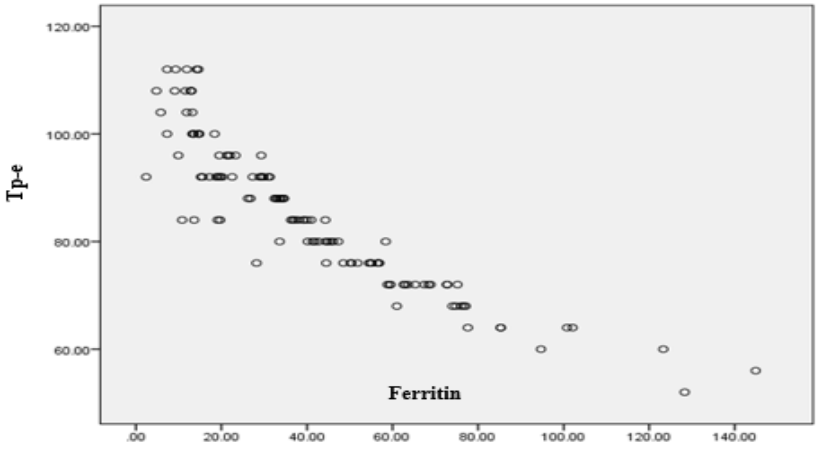

Fig.5: Tp-e changes in relation to ferritin

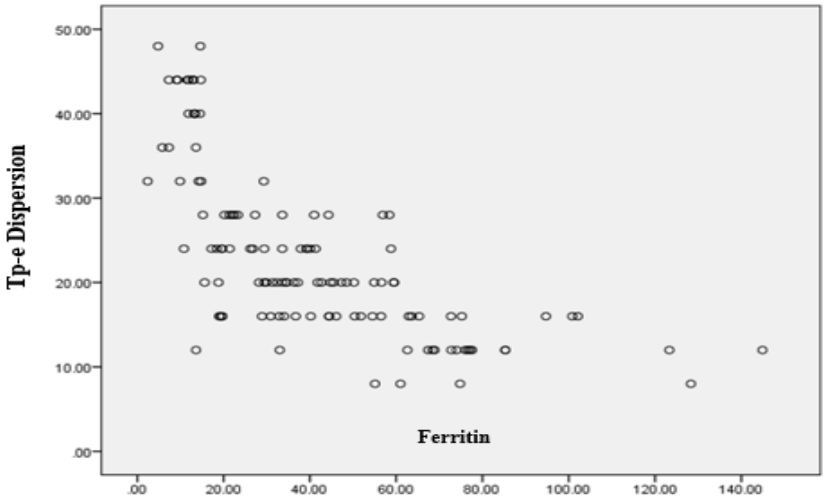

Fig.6: Tp-e Dispersion changes in relation to ferritin

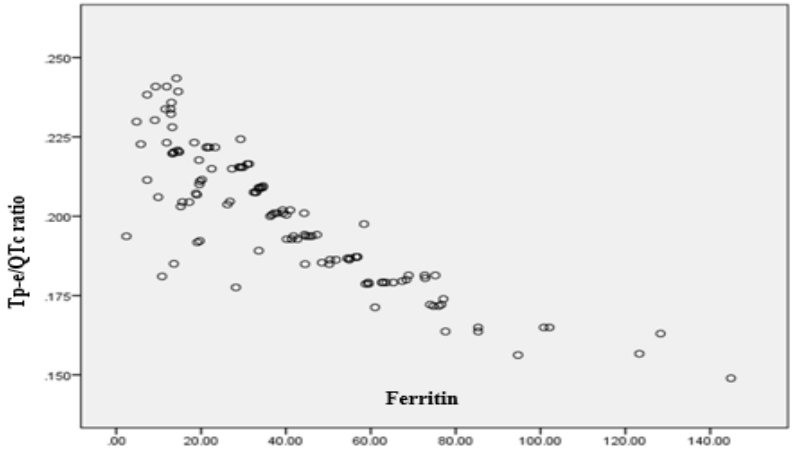

Fig.7: Tp-e/QTc ratio changes in relation to ferritin