

# Low Iron Stores in Otherwise Healthy Children Affect Electrocardiographic Markers of Important Cardiac Events

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**Abstract** Both an excess of iron and iron deficiency (ID) may lead to significant cardiac problems. Parameters that represent ventricular repolarization heterogeneity, like QT dispersion (QTd), corrected QT dispersion (QTcd), the interval between the peak and the end of the T wave (Tp-e), and Tp-e dispersion, have not been evaluated in otherwise healthy children with low iron levels before. Here we assessed the effects of low iron storage on P wave dispersion (PWd), QTd, Tp-e intervals, and Tp-e dispersion in otherwise healthy children. We prospectively reviewed 283 patients who were referred to pediatric cardiology department for cardiac evaluation due to murmurs and who were found to have no structural heart disease. The patients were divided into three groups according to their ferritin levels: Group 1: ferritin <15 ng/mL ( $n=58$ ); Group 2: ferritin 15–25 ng/mL ( $n=80$ ); Group 3: ferritin >25 ng/mL ( $n=145$ ). P wave duration (PW), QT and Tp-e intervals, and PW, QT, corrected QT (QTc), and Tp-e dispersions were significantly higher in patients whose ferritin level was <15 ng/mL. A negative correlation was found between ferritin level and QT and QTc intervals, and QT, QTc, and Tp-e dispersions. Our results showed that a low serum ferritin level is associated with changes in some ECG parameters such as prolonged PWd, Tp-e interval, QT, QTc, and Tp-e dispersions in otherwise healthy children, and studies of other populations indicated that these parameters may predict arrhythmias in selected patients. These patients

may be considered at some risk of developing arrhythmias. Therefore, careful evaluation of these ECG parameters is necessary in otherwise healthy children with low iron stores.

**Keywords** Anemia · Ferritin · Iron deficiency · Tp-e interval · Tp-e dispersion

## Introduction

Iron deficiency is the most common nutritional anemia worldwide, even in developed countries [1, 2]. In untreated individuals, iron deficiency anemia (IDA) will develop [1–3]. The clinical spectrum of IDA can range from asymptomatic to causing left ventricular dysfunction and severe heart failure [4]. Iron status is an important risk factor for cardiovascular health, as both an excess of iron and iron deficiency may lead to significant cardiac problems [5, 6]. Along with left ventricular dysfunction, some electrocardiographic (ECG) abnormalities such as sinus tachycardia, T wave and atrioventricular conduction abnormalities, and premature supraventricular and ventricular contractions have been described in adult populations with IDA [1, 7, 8]. Although there is little information on the subject, left ventricular systolic and diastolic dysfunction and sinus and atrial tachycardia have been reported in pediatric populations with anemia [9, 10].

Malignant ventricular arrhythmias (MVA) are the leading cause of sudden cardiac death (SCD). Although SCD due to MVA occurs frequently in patients with underlying heart disease, it also occurs in approximately 15–20% of individuals with structurally normal hearts [11]. With the recent advances in the field of cardiac electrophysiology, our understanding of the pathophysiological mechanisms

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of various diseases that lead to ventricular arrhythmias and SCD has improved. However, 12-lead surface electrocardiography (ECG) remains the most commonly used, easily accessible, and primary diagnostic tool. Previous studies have shown that some ECG markers representing atrial depolarization and ventricular repolarization, such as P wave dispersion (PWd) and QT dispersion (QTd), can predict the development of atrial and ventricular arrhythmias, respectively [12–15]. Increased QTd has been found among patients with MVA and SCD in different clinical conditions [14, 16, 17]. Aside from QT and QTc dispersions, new parameters derived from 12-lead surface ECG, such as the Tp-e interval, which is the measurement of the interval between the peak and the end of the T wave, and Tp-e dispersion have emerged as markers of transmural dispersion of repolarization (TDR) [18–20]. These parameters have been found to be highly useful in predicting ventricular arrhythmias in long QT syndrome, Brugada syndrome, and hypertrophic cardiomyopathy [21–23].

To date, some electrocardiographic changes such as prolonged QT and QTcd which are suggested as the marker of ventricular arrhythmia in patients with iron overload and prolonged P wave duration in patients with IDA have been reported [16, 24]. Parameters that represent the ventricular repolarization heterogeneity like QT, QTc dispersions, Tp-e interval, and Tp-e dispersion have not been evaluated in otherwise healthy children with low iron levels before.

This study is aimed to assess the effects of low iron storage on PWd, QTd, QTcd, Tp-e interval, and Tp-e dispersion in otherwise healthy children.

## Materials and Methods

### Study Population

This prospective study was conducted in the pediatric cardiology department of Dr. Behcet Uz Children's Hospital in Izmir, Turkey between June 2013 and September 2013. Included in this study were 283 patients who were referred to the pediatric cardiology department for cardiac evaluation due to murmurs, who had no structural heart disease with echocardiographic examination, and who had complete blood count, serum electrolytes, urea and creatinine, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), iron, and ferritin levels evaluated in a pediatric outpatient clinic. All participants were evaluated with a detailed physical examination and 12-lead surface electrocardiography. Excluded from the study were any patients with structural heart disease, congenital long QT syndrome, chronic illness (e.g., liver and kidney disease), hypo-hyperthyroidism, thalassemia, sickle cell anemia, or acute inflammatory illness; patients

who had bleeding disorders or were taking any medications such as digitals,  $\beta$ -blockers or any antiarrhythmic drugs, psychostimulant drugs; and patients who presented any electrolyte imbalance (hypo-hyponatremia, hypo-hyperkalemia, and hypo-hypercalcemia) that could affect heart rate and the QT interval. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethical committee of Dr. Behcet Uz Children's Hospital.

### Electrocardiography

A standard 12-lead ECG recording (Cardiofax GEM, Model 9022 K; Nihon Kohden, Tokyo, Japan) was performed with a speed of 25 mm/s and an amplitude of 1 mV/cm while the patients lay in a supine position. To increase the accuracy of the measurements, ECG recordings were scanned and transferred to a personal computer. After zooming in  $\times 400$  using Adobe Photoshop software, measurements were taken directly from these ECG tracings by a blind pediatric cardiologist who had no information about the patients' data. P wave duration was measured as the time between the beginning of the P wave (the point from the isoelectric line of the first visible upward slope for positive waves or the first visible downward slope for negative waves) and the ending point of the P wave (the point of return to the isoelectric line). The difference between the maximum and minimum of the P wave duration was defined as the PWd [24]. P waves from all 12 leads were used for calculation. PWd was not measured if less than nine leads were eligible for analysis.

The QT interval was defined as the measurement from the onset of the QRS complex to the end of the T wave. The end of the T wave was determined to be the intersection point of the isoelectric line and the tangent line at the maximum downward slope of the T wave. In the absence of the T wave, QT interval was not measured. Corrected QT interval was calculated using Bazett's formula. The QT dispersion was calculated in at least 8 of the 12 leads, which usually included lead I, II, and V5. The differences between the maximum and minimum QT and QTc intervals were defined as the QT and QTc dispersions, respectively [25, 26].

The Tp-e interval was measured as the duration from the peak of the T wave to the end of the T wave. We defined Te as the intersection point of the tangent to the downward slope of the T wave and the isoelectric line. All Tp-e measurements were taken from precordial leads. The dispersion of the Tp-e interval was calculated as the differences between the maximum and the minimum Tp-e intervals [27].

### Iron Status

Parameters for iron status included iron (Fe), serum ferritin, total iron-binding capacity (TIBC), hemoglobin (Hb), hematocrit (Hct), and mean cell volume (MCV). The blood samples were obtained in the morning, after at least 8 h of overnight fasting. ID was defined as a ferritin level of less than 15 ng/mL [28]. Ferritin was lower than 25 ng/mL was considered as low iron storage [29]. The patients were divided into three groups according to their ferritin levels (Group 1: ferritin <15 ng/mL; Group 2: ferritin 15–25 ng/mL; Group 3: ferritin >25 ng/mL).

### Statistical Analysis

The SPSS 18.0 package program was used (SPSS Inc., Chicago, IL, USA) for statistical analysis. The distribution pattern of data was evaluated using the Kolmogorov–Smirnov test. Values are expressed as mean ± SD or median (interquartile range) where appropriate. When compared with more than two independent groups, the ANOVA parametric test was used, and the Kruskal–Wallis test was used for abnormally distributed data. Chi-square analysis was used to compare categorical variables. Relationships between numeric variables were tested with Pearson or Spearman correlation analysis where appropriate. A *p* value <0.05 was considered statistically significant.

### Results

Study populations were divided into three groups according to their ferritin levels: Group 1: ferritin <15 ng/mL (*n*=58); Group 2: ferritin 15–25 ng/mL (*n*=80); Group 3: ferritin >25 ng/mL (*n*=145). The mean age of the study population was 11.1 ± 3.3 years. Of these patients, 120 were male and 163 were female.

Comparisons of the demographic and hematologic parameters of the three groups are shown in Table 1. The mean age of Group 1 was 11.2 ± 3.1 years, of Group 2 was 10.7 ± 3.8 years, and of Group 3 was 10.7 ± 3 years. The groups were similar in terms of age and gender. Hb, Hct, MCV, and Fe levels were significantly lower in group 1.

Electrocardiographic parameters of the groups are listed in Table 2. P wave duration, QT and Tp-e intervals, and PW, QT, QTc, and Tp-e dispersions were significantly higher in group 1. The median heart rate of Group 1 was 83 (35) bpm, of Group 2 was 94 (28) bpm, and of Group 3 was 88 (22) bpm; the groups were similar in terms of median heart rate.

A negative correlation was found between ferritin level and QT, QTc intervals, QT, and QTc and Tp-e dispersions. However, no correlation was found between ferritin levels and PW duration or PWd. Additionally, a negative correlation was found between Hct and both QT duration and Tp-e dispersions as well as between Hb levels and Tp-e dispersions (Table 3).

### Discussion

In this prospective study, we found that P wave, QT, Tp-e intervals, and PW, QT, QTc, and Tp-e dispersions were significantly prolonged in children with low ferritin levels. We found a significant negative correlation between both QT and QTc and Tp-e dispersions and serum ferritin levels.

Some ECG abnormalities such as atrial and ventricular premature contractions, supraventricular tachycardia, and sinus tachycardia have been reported in patients with low iron levels [1, 7]. Both QT and QTc dispersions reflect inhomogeneity of myocardial repolarization and hence were proposed as indicators of potential ventricular arrhythmias and SCD [14–17]. Authors of previous studies have stated that increased QT and QTc dispersions are

**Table 1** Comparison of the demographic and hematologic parameters of the groups

Variables	Group 1 ( <i>n</i> =58)	Group 2 ( <i>n</i> =80)	Group 3 ( <i>n</i> =145)	<i>p</i> value
Age (years) <sup>a</sup>	11.2 ± 3.1 (4–18)	10.7 ± 3.8 (3–18)	10.7 ± 3.0 (3–18)	0.6
Male/female ( <i>n</i> )	22/36	34/46	64/81	0.72
RBC (×10 <sup>6</sup> /mm <sup>3</sup> ) <sup>b</sup>	4.5 (0.6) (3.4–6.5)	4.6 (0.5) (3.8–5.5)	4.6 (0.5) (3.7–5.5)	0.73
Hemoglobin (g/dL) <sup>a</sup>	12.1 ± 1.3 (10–14)	12.8 ± 0.8 (10.8–14.8)	12.8 ± 0.9 (11–15.7)	<0.001
Hct (%) <sup>a</sup>	37 ± 3.2 (30–42)	39 ± 2.5 (34–44)	38.6 ± 2.6 (34–46)	<0.001
MCV (fL) <sup>a</sup>	80.2 ± 6.2 (70–86)	82.3 ± 5.4 (72–90)	83 ± 5.3 (75–90)	0.006
Fe (µg/dL) <sup>b</sup>	43 (34) (10–156)	75 (56) (45–205)	76 (51) (45–227)	0.001
TIBC (µg/dL) <sup>a</sup>	391 ± 65 (230–495)	340 ± 66 (212–480)	317 ± 64 (98–461)	<0.001

*n* number of subjects, *RBC* red blood cells, *Hct* hematocrit, *MCV* mean cell volume, *Fe* iron, *TIBC* total iron-binding capacity

<sup>a</sup>Parameters are shown as mean ± standard deviation (minimum–maximum)

<sup>b</sup>Parameters are shown as median (interquartile range) (minimum–maximum)

**Table 2** Comparison of the electrocardiographic parameters of the three groups

Variables	Group 1 (n=58)	Group 2 (n=80)	Group 3 (n=145)	p value
Heart rate (bpm) <sup>a</sup>	83 (35) (58–136)	94 (28) (54–132)	88 (22) (50–128)	0.11
P wave (ms) <sup>b</sup>	91 ± 21 (60–140)	84 ± 12 (60–120)	86.2 ± 17.2 (40–120)	0.04
QT interval (ms) <sup>b</sup>	375 ± 45 (280–460)	353.5 ± 38 (300–440)	348 ± 40 (280–440)	<0.001
QTc interval (ms)	423 ± 25.2 (344–450)	421 ± 16.4 (320–440)	414 ± 24 (340–440)	0.07
Tp-e interval (ms) <sup>b</sup>	97 ± 18.7 (60–130)	91 ± 21 (50–130)	89 ± 16 (50–120)	0.03
PW dispersion (ms) <sup>b</sup>	65.8 ± 23.6 (30–110)	55 ± 14 (10–100)	57 ± 18 (20–100)	0.02
QT dispersion (ms) <sup>b</sup>	69.4 ± 39 (20–120)	57.6 ± 25.5 (20–110)	51.6 ± 19.3 (20–100)	0.02
QTc dispersion (ms)	72.8 ± 42.2 (10–130)	66 ± 30.2 (15–130)	61.6 ± 23.7 (22–130)	0.04
Tp-e dispersion (ms) <sup>b</sup>	63 ± 21 (20–100)	56 ± 16 (20–100)	55 ± 15 (20–100)	0.03

bpm beat per minute, ms milliseconds, n number of subjects, QTc corrected QT interval

<sup>a</sup>Parameters are shown as median (interquartile range) (minimum–maximum)

<sup>b</sup>Parameters are shown as mean ± standard deviation (minimum–maximum)

**Table 3** Correlation between ferritin, hematocrit, hemoglobin levels, and electrocardiographic parameters

		PW	QT	QTc	Tp-e	PWd	QTd	QTcd	Tp-e dis.
Ferritin	r	−0.04	−0.21	−0.11	−0.1	−0.03	−0.18	−0.10	−0.12
	p	0.41	<0.001	0.03	0.07	0.11	0.02	0.04	0.03
Hematocrit	r	0.04	−0.13	−0.06	0.05	−0.06	0.09	0.02	−0.15
	p	0.44	0.01	0.23	0.32	0.09	0.09	0.68	0.008
Hemoglobin	r	0.07	−0.1	−0.07	0.06	−0.04	0.1	0.03	−0.19
	p	0.18	0.07	0.18	0.29	0.12	0.08	0.51	0.001

significantly correlated with the incidence of premature ventricular contractions (PVCs) in children with structurally normal hearts [30]. Although increased QT and QTc dispersions have occurred in patients with high iron stores under different clinical conditions [16, 31], these parameters have not previously been studied in otherwise healthy children with low iron storage. In a study that evaluated 43 children with breath-holding spells, researchers found significantly higher QT and QTc dispersions in patients with breath-holding spells than in the healthy controls; however, they could not find any association between iron deficiency and these parameters [32]. In contrast to these results, in this prospective study, we found significantly higher QT and QTc dispersions in cases with low iron stores compared to normal levels, and we found significant negative correlation between ferritin levels and QT and QTc dispersions. However, we did not find any correlation between Hb, Hct levels, and QT and QTc dispersions.

Recently reported studies have showed that the last part of the T wave represents the arrhythmogenic tendency for ventricular arrhythmias and SCD. The interval between the peak and the end of the T wave (Tp-e interval) and Tp-e dispersion show the dispersion of ventricular repolarization, and these parameters are more useful markers of TDR compared to QT dispersion [18, 19, 23]. Prolonged Tp-e interval and Tp-e dispersion were demonstrated in different clinical conditions, such as long QT syndrome, Brugada

syndrome, hypertrophic cardiomyopathy, and myocardial infarction [18–23, 33]. In one study, prolonged Tp-e intervals and Tp-e dispersions were found to be associated with inducible ventricular tachycardia (VT) and ventricular fibrillation (VF) at electrophysiological study in patients with Brugada syndrome [34]. Given that Tp-e interval and Tp-e dispersion have not been evaluated in children with low iron levels before, in the current study we found prolonged Tp-e intervals and Tp-e dispersions in children with low iron levels and a negative correlation between Tp-e dispersion and ferritin, Hb, and Hct levels.

Studies have shown that P wave dispersion is an important noninvasive ECG marker for assessing the homogeneous distribution of sinus node impulses through the atrial myocardium [12, 13]. The predictive value of PWd in atrial flutter and fibrillation has been shown both in cases without underlying heart disease and in those with different cardiac conditions. Studies on pediatric and young adult patients have showed that both P wave duration and PWd are affected by factors such as age, heart rate, body weight, body mass index (BMI), and exercise status [35, 36]. BMI is one of the most important determinants of the left atrial size. Increase in size and mass of the atrium may contribute to the increase in P wave duration and PWd. In addition, some electrolyte imbalances, tissue hypoxia, and alterations in cardiac autonomic tone may also influence P wave duration and PWd [12, 13, 24]. Simsek et al. [24] reported

that ID is associated with prolonged P wave duration and PWd. The authors stated that these changes may be attributed to tissue hypoxia, altered cardiac autonomic tone, and increased sympathetic activity due to IDA. Like this study, we found prolonged P wave duration and dispersion in children with low iron stores; however, we did not find any correlation between these parameters and ferritin level. Although there was no statistically significant difference between our groups in terms of age, the wide age range of our patient groups in combination with the aforementioned factors such as body weight, BMI, and exercise status may have affected these parameters to some extent and may explain why we did not find any correlation between these parameters and ferritin levels.

Links between anemia, iron deficiency, and impaired cardiovascular hemodynamics have been described in previous studies [1, 4, 5]. Anemia has been identified as an independent risk factor for adverse cardiac outcomes [5, 24]. Studies have connected chronic untreated anemia or ID with hyper-dynamic cardiac states that result in increased cardiac output, cardiac sympathetic activation, and some pathological changes in ventricular geometry and ventricular functions [1, 4]. Correction of the iron deficiency, even before a rise in hemoglobin levels, improves cardiac function and autonomic imbalance [37]. Structural changes in the atrial and ventricular myocardium together with altered autonomic balance may be associated with increased P waves, QT, Tp-e intervals, and QTc and Tp-e dispersions. Therefore, we consider that possible structural myocardial changes, reduced tissue oxygenation, and alterations in autonomic tone due to low iron stores may lead to increased PWd, QTd, Tp-e interval, and Tp-e dispersion in our study. Due to the lack of data evaluating the aforementioned non-invasive ECG parameters in otherwise healthy children with low iron stores, this prospective study may contribute some clinical implications related to the tendency of fatal ventricular arrhythmias. Our findings may also be a starting point for further clinical and electrophysiological studies in these populations.

The current study has some limitations; the relatively small sample size of the iron deficiency group (Group 1), most notably, is a major limitation of our study. Although we selected similar age groups to minimize the effect of age on heart rate and ECG parameters, we did not compare the patient groups in terms of body weight or BMI, and we did not evaluate the exercise status of the patients, which can affect heart rate and the ECG parameters. Additionally, although our patient groups were not statistically different in terms of age, and the wide age range of our patient groups may have affected the ECG parameters to some extent. We did not evaluate the correlation between QT, QTc, Tp-e dispersions, and PVCs in ID subjects. We could not prospectively follow up with subjects with ID to

check for atrial and ventricular arrhythmias, and therefore we could not evaluate these parameters for future atrial and ventricular arrhythmic events. Lastly, we could not compare the electrocardiographic parameters of subjects with ID before and after undergoing iron replacement therapy.

In conclusion, our results showed that low serum ferritin level is associated with changes in some ECG parameters such as prolonged PWd, Tp-e interval, QT, and QTc and Tp-e dispersions in otherwise healthy children, and studies of other populations indicated that these parameters may predict arrhythmias in selected patients. These patients may be considered at some risk of developing arrhythmias. Therefore, careful evaluation of these ECG parameters is necessary in otherwise healthy children with low iron stores. Further, prospective electrophysiological studies using 24-h ECG monitoring are needed to exhibit the clinical usefulness and prognostic implications of these parameters before and after iron replacement therapy.

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#### Compliance with Ethical Standards

**Conflict of interest** The authors declare no conflict of interest.

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