ORIGINAL ARTICLE

Impact of Iron and Homocysteine Levels on T Peak-to-End Interval and Tp-e/QT Ratio in Elite Athletes

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Background: Electrocardiography (ECG) is frequently used in preparticipation evaluation of competitive athletes. Repolarization heterogeneities on ECG is a well-known indicator for malignant ventricular arrhythmias and sudden cardiac death. We aimed to investigate the effect of iron and homocysteine levels on arrhythmogenic indicators, T peak-to-end (Tp-e) interval, and Tp-e/QT ratio in elite athletes.

Methods: A total of 72 players (48 football and 24 basketball) with a mean age of 25.4 ± 5.0 years were included to the analysis. Blood biochemistry, homocysteine level, and iron parameters (transferrin saturation and serum iron) were obtained by standard methods. Duration of QRS, QT interval, and Tp-e interval were measured manually on the precordial leads and Tp-e/QT ratio was calculated.

Results: Baseline demographic and clinical characteristics of the study population were compared in two groups according to the median value of $Tp-e/QT = 0.219$. Both iron and transferrin saturations were higher in the above median group ($P = 0.001$ and $P = 0.002$, respectively), however, homocysteine levels were not statistically different among two groups ($P = 0.405$). In correlation analysis, both serum iron and transferrin saturation were significantly correlated with Tp-e interval ($r = 0.368$; $P = 0.001$ and $r = 0.394$; $P = 0.00$, respectively) and Tp-e/QT ratio ($r = 0.357$; $P = 0.002$ and $r = 0.372$; $P = 0.001$, respectively). Multiple stepwise regression analysis revealed that transferrin saturation was an independent predictor of Tp-e interval and Tp-e/QT ratio ($\beta = 0.325$; $P = 0.002$ and $\beta = 0.372$; $P = 0.001$, respectively).

Conclusion: This study showed an independent relationship between iron status and Tp-e interval and Tp-e/QT ratios of elite sport players which were also not correlated with serum homocysteine levels.

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Tp-e interval; homocysteine; iron; athlete; arrhythmia

Sudden cardiac death in young competitive athletes is an important public health issue which highly attracts community attention. A substantial portion of these deaths is attributable to cardiac arrhythmias in subjects with normal heart. Current evidence suggests that the use of a practical and

effective screening protocol for preparticipation evaluation of competitive athletes has significantly reduced mortality in this vulnerable population.¹ Electrocardiography (ECG) is frequently used in preparticipation evaluation of competitive athletes. Repolarization heterogeneities on ECG is a

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well-known indicator for malignant ventricular arrhythmias and sudden cardiac death.² The T peak-to-end (Tp-e), which is the interval between the peak and the end of T wave on electrocardiogram, and the Tp-e/QT ratio are novel electrocardiographic indexes of total dispersion of ventricular repolarization. These well-appreciated indicators of increased dispersion of ventricular repolarization are also shown to be related to malign arrhythmias in conditions such as structural heart disease, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, and acute myocardial infarction.²⁻⁴

Homocysteine is a modified amino acid and accumulation in the circulation may induce pathological consequences. Elevated homocysteine levels are associated with atherosclerosis, coronary artery disease, acute myocardial infarction, cardiac arrhythmias, and sudden cardiac death.^{5,6} Homocysteine has deleterious effects on membrane-associated proteins including ion channels and gap junctions by increasing oxidative stress, thereby inducing extracellular matrix remodeling. These evidences suggest that homocysteine may alter cell excitability and facilitate initiation of arrhythmias. Iron is involved in several important processes such as oxygen delivery, free radical formation, and immunity. Both deficiency and excess of iron in the body may end up with severe deterioration in the metabolism. Increased levels of iron in the myocardium may increase QT dispersion, hence rise in the risk of arrhythmias.⁷

In this study, we aimed to investigate the effect of iron and homocysteine levels on novel arrhythmogenic indicators, Tp-e interval, and Tp-e/QT ratio, in a specific group of subjects, elite athletes, who are highly remarkable for cardiovascular risks and sudden cardiac death.

METHODS

Participants

Data of a total of 90 young male elite football and basketball players (age: 16–38 years) who had applied to Acibadem Ankara Hospital for medical checkup in the period between 2014 and 2015 were collected and analyzed. All the participants were professional players in sports clubs (three football and three basketball teams), which participate in related national leagues. All of the participants

were involved in active sport training in some form once or twice a day for at least 6 days of each week. Each player had a cardiovascular evaluation carried out by the same cardiologist, which included personal and family history, physical examination, ECG, and echocardiography. Body measurements, urine and blood tests were also performed according to standard protocols. None of the participants had a history of hypertension, coronary artery disease, diabetes mellitus, renal or hepatic failure or a family history of hypertrophic cardiomyopathy, or unexplained sudden cardiac death. Exclusion criteria were; acute metabolic or electrolyte disturbance, thyroid dysfunction, active inflammation, any medication likely to influence the investigated parameters, excessive noise on the electrocardiographic signal that precludes analysis of the ECG waveform, alcohol or coffee consumption within 12 hours. After exclusion, 72 players were eligible for the study and statistical analysis was executed in this study group. Study was approved by Acibadem University Medical Ethics Committee.

Biochemical Analysis, Electrocardiography, and Echocardiography

Blood samples were obtained by venipuncture in the cubital fossa under aseptic conditions after 12-hour fasting and immediately transported to the adjacent laboratory for analysis. Sysmex XT 2000i Automated Hematology analyzer (SYSMEX Corp., Hyogo, Japan) was utilized for complete blood count. Blood biochemistry, homocysteine level, and iron parameters (transferrin saturation and serum iron) were obtained by standard methods (Roche Integra 400, Roche Diagnostics Ltd., Rotkreuz, Switzerland) by using commercial kits. Estimated glomerular filtration rate was calculated according to CKD-EPI formula.

Resting 12-lead ECG (MAC 1200, GE Healthcare, Milwaukee, WI, USA) with a paper speed of 10 mm/s and gain of 20 mm/mV was used for analysis. Duration of QRS, QT interval, and Tp-e interval were measured manually on the precordial leads with a caliper and Tp-e/QT ratio was calculated from these measurements. Measurement of QT interval was made according to previously described methods and QT interval was corrected for heart rate using Bazett formula.⁸ Tp-e interval was defined as the interval from

Figure 1. Measurement of Tp-e interval that was defined as the interval from the peak of T wave to the end of T wave. End of the T wave was defined as the intersection of the tangent to the T wave and the isoelectric line.

the peak of T wave to the end of T wave (Fig. 1). End of the T wave was defined as the intersection of the tangent to the T wave and the isoelectric line. Maximum of the Tp-e interval in all six precordial leads was reported according to previously described method.⁴

Echocardiographic evaluations were performed using a commercially available device (Vivid 7 pro, GE Vingmed, Horten, Norway). Left ventricle diameters and wall thicknesses were measured from parasternal long axis view. Left ventricle ejection fraction was obtained by using modified Simpson method. The LV mass was calculated using the Devereux formula.⁹

Statistical Analysis

Data management and all statistical analyses were performed by using the SPSS for Windows Version 22.0 package program (Chicago, IL, USA). Continuous variables were expressed as mean $\pm$ standard deviation or median (minimum-maximum) as appropriate. Parametric test assumptions (normality and homogeneity of variance) were tested before groups were compared for continuous variables. Shapiro-Wilks test was used when continuous variables were not normally distributed. Homogeneity of variances was tested using Levine test. Continuous variables were tested with *t*-test or Mann-Whitney U test as appropriate. Categorical variables were evaluated with chi-square test or Fisher's exact test. Differences across tertiles of transferrin saturation were tested with one-way ANOVA or Kruskal-Wallis test as appropriate. Univariate correlation and multiple linear regression analyses were used

to determine the possible confounding factors for the Tp-e and Tp-e/QT ratio. Variables with a P value of <0.2 in univariate regression analysis were tested in the multiple regression models. Tp-e was used as a continuous variable in multiple regression analysis. A P value less than 0.05 was considered statistically significant.

RESULTS

A total of 72 players (48 football and 24 basketball) with a mean age of 25.4 ± 5.0 years were included in the analysis. Baseline demographic and clinical characteristics of the study population were compared in two groups according to the median value of $Tp-e/QT = 0.219$ and these parameters were presented in Table 1. The mean Tp-e interval was 83.6 ± 15.6 ms and the mean Tp-e/QT ratio was 0.221 ± 0.36 in the whole population. There were no statistically significant differences between groups in terms of age, type of game participated, weight, height, body mass index (BMI), and echocardiographical parameters. Laboratory parameters of blood glucose, sodium, potassium, calcium, magnesium, creatinine, estimated glomerular filtration rate (eGFR), triglyceride, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), lactate dehydrogenase (LDH), c-reactive protein (CRP), and thyroid-stimulating hormone (TSH) levels were also statistically similar among the groups. Hemoglobin levels and platelet counts are comparable among the groups while leukocyte counts were higher in the above median group

Table 1. Demographic and Clinical Data of the Overall Study Population and of the Two Groups with Tp-e/QT above (≥ 0.219) and below (< 0.219) the Median Value

	All Participants (n = 72)	Tp-e/QT <0.219 (n = 36)	Tp-e/QT ≥ 0.219 (n = 36)	P
Age, years	25.4 $\pm$ 5.0	24.9 $\pm$ 4.9	25.9 $\pm$ 5.2	0.419
Football/basketball	48/24	21/15	27/9	0.211
Weight, kg	83.4 $\pm$ 12.8	83.4 $\pm$ 12.5	83.4 $\pm$ 13.3	0.993
Height, m	1.86 $\pm$ 0.1	1.87 $\pm$ 0.1	1.85 $\pm$ 0.1	0.371
BMI, kg/m ²	24.1 $\pm$ 1.6	23.7 $\pm$ 1.7	24.2 $\pm$ 1.6	0.198
Laboratory parameters				
Glucose, mg/dl	89.9 $\pm$ 8.7	90.8 $\pm$ 7.7	89 $\pm$ 9.7	0.371
Sodium, mmol/l	139.5 $\pm$ 1.9	139.2 $\pm$ 2.1	140 $\pm$ 1.7	0.089
Potassium, mmol/l	4.3 $\pm$ 0.3	4.3 $\pm$ 0.3	4.3 $\pm$ 0.3	0.910
Calcium, mg/dl	9.65 $\pm$ 0.3	9.7 $\pm$ 0.3	9.6 $\pm$ 0.3	0.710
Magnesium, mg/dl	2.0 $\pm$ 0.2	2.0 $\pm$ 0.2	2.1 $\pm$ 0.3	0.228
Creatinine, mg/dl	0.96 $\pm$ 0.11	0.95 $\pm$ 0.11	0.97 $\pm$ 0.11	0.874
eGFR, ml/min/1.73 m ²	106.8 $\pm$ 11.7	108.1 $\pm$ 12.6	105.6 $\pm$ 10.8	0.369
Triglyceride, mg/dl	71 [25–302]	71 [38–302]	70 [25–222]	0.964
Total cholesterol, mg/dl	168.4 $\pm$ 34.7	169.1 $\pm$ 35.8	167.8 $\pm$ 34.2	0.877
HDL, mg/dl	52.4 $\pm$ 16.7	54.7 $\pm$ 21.3	50.2 $\pm$ 10	0.255
LDL, mg/dl	109.8 $\pm$ 29.3	109.9 $\pm$ 28.9	109.8 $\pm$ 30.2	0.987
LDH, U/l	194.3 $\pm$ 44.2	187.7 $\pm$ 35.1	201 $\pm$ 51.4	0.202
C-reactive protein, mg/dl	0.08 [0.02–0.90]	0.09 [0.02–0.90]	0.07 [0.02–0.38]	0.387
TSH, uIU/ml	2.5 $\pm$ 0.9	2.5 $\pm$ 1	2.5 $\pm$ 0.9	0.822
Homocysteine, μ mol/l	10.9 [5.5–43.2]	10.6 [5.5–43.2]	12.5 [6.4–37.1]	0.405
Iron, μ g/dl	107.10 $\pm$ 42.8	91.4 $\pm$ 29.8	122.8 $\pm$ 48.1	0.001
Transferrin saturation, %	34.33 $\pm$ 13.5	29.5 $\pm$ 10.3	39.2 $\pm$ 14.6	0.002
Leukocyte, $\times 10^3/\mu$ l	6.0 $\pm$ 1.3	5.6 $\pm$ 1.4	6.4 $\pm$ 1.1	0.007
Hemoglobin, g/dl	15.2 $\pm$ 1.5	15.1 $\pm$ 2	15.3 $\pm$ 0.8	0.482
Platelet, $\times 10^3/\mu$ l	208.6 $\pm$ 35.9	209.9 $\pm$ 33.5	207.3 $\pm$ 38.7	0.755
Conventional echocardiographic parameters				
LVEDD, mm	48.9 $\pm$ 2.6	49.1 $\pm$ 2.8	48.8 $\pm$ 2.5	0.688
LVESD, mm	32.8 $\pm$ 1.9	33 $\pm$ 2	32.7 $\pm$ 1.8	0.502
LVEF, %	61.4 $\pm$ 2.2	61.3 $\pm$ 2.1	61.5 $\pm$ 2.3	0.790
Left atrium, mm	35.8 $\pm$ 1.5	36.1 $\pm$ 1.5	35.5 $\pm$ 1.4	0.096
IVS, mm	10 [8–12]	10 [8–12]	11 [9–12]	0.138
PW, mm	10 [9–12]	10 [9–12]	10 [9–12]	0.597
LV mass, g	188.9 $\pm$ 30.4	187.2 $\pm$ 29.8	190.5 $\pm$ 31.4	0.648
Electrocardiographic parameters				
Heart rate, beat/min	75.1 $\pm$ 11.5	73.1 $\pm$ 13.2	77.3 $\pm$ 9.1	0.117
QT interval, ms	376.81 $\pm$ 25.8	375.4 $\pm$ 22.1	378.2 $\pm$ 29.2	0.651
QTc interval, ms	419.1 $\pm$ 30.2	411.1 $\pm$ 27.4	427.2 $\pm$ 31.1	0.023
Tp-e interval, ms	83.6 $\pm$ 15.6	72.6 $\pm$ 7.1	94.6 $\pm$ 14.0	<0.001
Tp-e/QT ratio	0.221 $\pm$ 0.36	0.193 $\pm$ 0.017	0.249 $\pm$ 0.027	<0.001
PR	168 [140–200]	165 [140–200]	168 [140–200]	0.905
QRS	90 [70–110]	90 [70–110]	90 [70–110]	0.971

Variables were expressed as mean $\pm$ standard deviation or median (minimum-maximum) as appropriate.

eGFR = estimated glomerular filtration rate according to CKD-EPI formula; HDL = high-density lipoprotein; IVS = interventricular septum; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; LV = left ventricle; LVEDD = left ventricle end diastolic diameter; LVEF = left ventricle ejection fraction; LVESD = left ventricle end systolic diameter; Tp-e = T peak-to-end; TSH = thyroid-stimulating hormone.

($P = 0.007$). Resting heart rate and QT intervals were similar among groups but, corrected QT interval was significantly longer in higher Tp-e/QT group ($P = 0.022$). Both iron and transferrin saturations were higher in the above median

group ($P = 0.001$ and $P = 0.002$, respectively), however, homocysteine levels were not statistically different among two groups ($P = 0.405$).

Since transferrin saturation was very closely correlated with iron level ($r = 0.951$, $P < 0.001$),

Table 2. Iron Parameters, Homocysteine Levels, Tp-e Interval and Tp-e/QT Ratio by Tertiles of Transferrin Saturation

	Tertile 1 Transferrin Saturation <28% (n = 23)	Tertile 2 Transferrin Saturation 28–39% (n = 26)	Tertile 3 Transferrin Saturation >39% (n = 23)	P^a
Iron, $\mu\text{g/dl}$	67.8 $\pm$ 17.7	101.2 $\pm$ 16.2	153.1 $\pm$ 37.7	<0.001
Transferrin saturation, %	20.8 $\pm$ 4.8	32.8 $\pm$ 3.4	49.6 $\pm$ 10.6	<0.001
Homocysteine, $\mu\text{mol/l}$	10.2 [5.5–43.2]	10.9 [6.4–38.0]	12.4 [6.8–23.8]	0.643
Tp-e interval, ms	76.5 $\pm$ 8.8	83.3 $\pm$ 17.5	91.1 $\pm$ 15.9	0.005
Tp-e/QT ratio	0.203 $\pm$ 0.023	0.223 $\pm$ 0.041	0.238 $\pm$ 0.032	0.003
PR interval, ms	169.1 $\pm$ 15.7	170.2 $\pm$ 17.6	164.4 $\pm$ 17.3	0.451
QRS duration, ms	92.0 $\pm$ 7.5	88.3 $\pm$ 8.1	90.0 $\pm$ 9.7	0.319
Heart rate, bpm	73.0 $\pm$ 11.3	76.8 $\pm$ 10.8	75.6 $\pm$ 12.4	0.503
QTc interval, ms	414.1 $\pm$ 34.6	418.2 $\pm$ 27.5	425.3 $\pm$ 28.5	0.451

bpm = beta per minute; QTc = corrected QT; Tp-e = T peak-to-end.

^aOne-way ANOVA or Kruskal-Wallis.

for simplicity, we use only transferrin saturation tertiles (Tertile 1 transferrin saturation <28%, Tertile 2 transferrin saturation 29–38%, Tertile 3 transferrin saturation >38%) to determine the trends of Tp-e interval, Tp-e/QT ratio, and homocysteine levels according to iron status (Table 2). Tp-e interval and Tp-e/QT ratio were significantly increased in higher tertiles of transferrin saturation (Tp-e interval by transferrin saturation tertiles; 76.5 $\pm$ 8.8 ms vs 83.3 $\pm$ 17.5 ms vs 91.1 $\pm$ 15.9 ms, $P = 0.005$ and Tp-e/QT ratio by transferrin saturation tertiles; 0.203 $\pm$ 0.023 vs 0.223 $\pm$ 0.041 vs 0.238 $\pm$ 0.032, $P = 0.003$, respectively) see also Figure 2. However, homocysteine levels did not differ significantly among these tertile groups ($P = 0.643$). Also, PR interval, QRS duration, heart rate, and QTc interval were not statistically different between tertile groups ($P = 0.451$, $P = 0.319$, $P = 0.503$ and $P = 0.451$, respectively).

In correlation analysis, age and LDH were correlated with Tp-e interval ($r = 0.236$; $P = 0.046$ and $r = 0.254$, $P = 0.031$, respectively) significantly, however, these correlations were not statistically significant for Tp-e/QT ratio ($r = 0.182$; $P = 0.127$ and $r = 0.212$; $P = 0.074$). Both serum iron and transferrin saturation were significantly correlated with Tp-e interval ($r = 0.368$; $P = 0.001$ and $r = 0.394$; $P = 0.001$, respectively) and Tp-e/QT ratio ($r = 0.357$; $P = 0.002$ and $r = 0.372$; $P = 0.001$, respectively), see Figure 3. On the other hand, correlation among homocysteine, Tp-e interval, and Tp-e/QT ratio was not statistically significant ($r = -0.014$; $P = 0.904$ and $r = -0.061$, $P = 0.608$, respectively).

Figure 2. Tp-e interval and Tp-e/QT ratio by transferrin saturation tertiles.

Figure 3. Correlation between Tp-e interval and transferrin saturation.

No significant correlations were observed among echocardiographic parameters Tp-e interval and Tp-e/QT ratio. QTc interval was correlated with sodium, calcium, creatinine, and eGFR ($r = 0.329$; $P = 0.005$, $r = 0.274$; $P = 0.02$, $r = 0.326$; $P = 0.005$ and $r = -0.305$; $P = 0.009$, respectively). QTc interval was not significantly correlated with transferrin saturation and iron ($r = 0.215$; $P = 0.069$ and $r = 0.193$; $P = 0.104$; Table 3). QRS duration was not significantly correlated with any of the parameters except leukocyte count ($r = 0.272$; $P = 0.021$).

Multiple stepwise regression model taking Tp-e interval as dependent variable and age, QT interval, QTc interval, glucose, TSH, BMI, LDH, eGFR, transferrin saturation, and serum iron as independent variable revealed that QT interval and transferrin saturations were independently associated with Tp-e interval ($\beta = 0.407$; $P < 0.001$ and $\beta = 0.325$; $P = 0.002$, respectively). Additionally, in multiple stepwise regression model taking Tp-e/QT ratio as independent variable and age, QTc interval, heart rate, BMI, LDH, leukocyte count, interventricular septum thickness, serum iron, and transferrin saturation as independent variables, transferrin saturation was found to be an independent predictor of Tp-e/QT ratio ($\beta = 0.372$; $P = 0.001$). Besides, in multiple stepwise regression model taking QTc interval as dependent variable and sodium, potassium, magnesium, calcium as

potential confounders and also creatinine and transferrin saturation as independent variables. In this regression model, transferrin saturation was found as a weaker but an independent predictor of QTc interval together with sodium and creatinine ($\beta = 0.221$; $P = 0.039$, $\beta = 0.311$; $P = 0.004$ and $\beta = 0.299$; $P = 0.006$, respectively).

DISCUSSION

In this study, we demonstrated an independent relationship between iron status and Tp-e interval and Tp-e/QT ratios of elite sports players which were also independent from serum homocysteine levels. Increased iron levels were associated with longer Tp-e interval and higher Tp-e/QT ratios.

Identification of subjects who are prone to sudden cardiac death within a low-risk population such as athletes is very demanding and development of novel markers is crucial. Preparticipation screening has been associated with a significant decline in the incidence and mortality of sudden cardiac death events in young athletes.¹ Screening for cardiovascular risk should involve inexpensive and easily obtainable parameters and indices. Current data propose that the Tp-e interval and Tp-e/QT ratio are well-appreciated markers of increased dispersion of ventricular repolarization which are more sensitive arrhythmogenic indices compared to older index, QT dispersion.¹⁰ However, Tp-e interval and Tp-e/QT ratio are not tested adequately in athletes and hitherto, there is only one study evaluating these indices in athletes.¹¹ Our study would provide additional data related with indices of total dispersion of repolarization in athletes. Prognostic value of these indices would also be evaluated in athletes prospectively.

In daily practice, free iron, serum ferritin, and transferrin saturation are commonly used to assess iron status of the subjects. Transferrin saturation is an acceptable screening tool and prognostic marker which is relatively inexpensive and simple venous blood test with increasing body of evidence suggesting use of transferrin saturation in cardiovascular risk stratification.¹² In our study, we used transferrin saturation and serum iron levels to evaluate the iron status of study population.

Iron hypothesis was first proposed by Sullivan more than three decades ago, which implies the lower cardiovascular risk in premenopausal

Table 3. Correlation between Tp-e Interval, Tp-e/QT Ratio, QTc, Demographic and Clinical Variables

	Tp-e		Tp-e/QT		QTc	
	Correlation Coefficient	P	Correlation Coefficient	P	Correlation Coefficient	P
Age	0.236	0.046	0.182	0.127	0.066	0.581
Weight	0.065	0.589	0.099	0.410	0.091	0.445
Height	-0.027	0.821	0.015	0.900	0.048	0.687
BMI	0.184	0.123	0.177	0.137	0.135	0.257
Laboratory parameters						
Glucose	-0.214	0.071	-0.143	0.232	-0.034	0.780
Sodium	0.050	0.675	0.030	0.804	0.329	0.005
Potassium	0.075	0.532	0.033	0.780	0.087	0.468
Calcium	-0.088	0.463	-0.088	0.460	0.274	0.020
Magnesium	0.159	0.183	0.130	0.275	0.119	0.320
Creatinine	0.125	0.295	0.068	0.570	0.326	0.005
eGFR	-0.183	0.123	-0.145	0.225	-0.305	0.009
Triglyceride	-0.076	0.526	-0.056	0.642	0.009	0.940
Total cholesterol	0.042	0.724	-0.023	0.850	0.047	0.696
HDL	-0.139	0.246	-0.122	0.308	-0.014	0.907
LDL	0.052	0.663	-0.037	0.757	0.049	0.681
LDH	0.254	0.031	0.212	0.074	0.099	0.406
C-reactive protein	-0.031	0.797	-0.081	0.500	-0.070	0.556
TSH	0.160	0.181	0.132	0.270	-0.043	0.721
Homocysteine	-0.014	0.904	-0.061	0.608	0.013	0.913
Iron	0.368	0.001	0.357	0.002	0.193	0.104
Transferrin saturation	0.394	0.001	0.372	0.001	0.215	0.069
Leukocyte	0.144	0.226	0.223	0.060	0.046	0.704
Hemoglobin	0.016	0.896	0.057	0.634	-0.160	0.181
Platelet	-0.077	0.518	-0.085	0.478	0.136	0.255
Conventional echocardiographic parameters						
LVEDD	-0.033	0.780	0.033	0.783	-0.123	0.304
LVEDS	-0.053	0.659	0.026	0.830	-0.046	0.701
LVEF	0.058	0.631	0.007	0.954	-0.077	0.518
Left atrium	-0.096	0.423	-0.098	0.412	-0.050	0.677
IVS	0.132	0.269	0.193	0.105	-0.035	0.771
PW	0.089	0.459	0.109	0.361	-0.045	0.708
LV mass	0.069	0.564	0.130	0.276	-0.092	0.440
Electrocardiographic parameters						
Heart rate	-0.030	0.802	0.180	0.130	0.548	<0.001
QT interval	0.462	<0.001	0.098	0.414	0.409	<0.001
QTc interval	0.410	<0.001	0.283	0.016	-	-
PR	0.139	0.245	0.118	0.323	-0.145	0.226
QRS	0.011	0.929	-0.038	0.754	0.052	0.662

eGFR = estimated glomerular filtration rate according to CKD-EPI formula; HDL = high-density lipoprotein; IVS = interventricular septum; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; LV = left ventricle; LVEDD = left ventricle end diastolic diameter; LVEF = left ventricle ejection fraction; LVEDS = left ventricle end systolic diameter; Tp-e = T peak-to-end; TSH = thyroid-stimulating hormone.

Pearson's and Spearman's tests were used for correlation analysis.

women compared to men and postmenopausal women processing higher iron stores. This difference in the cardiovascular risk was attributed to the periodical loss of iron during menstruation.¹³ In addition, recent studies enounce that homocysteine causes vascular damage via an iron-dependent

pathway.¹⁴ Despite the conducted studies to date, debates concerning these hypotheses still persist. In this context, we evaluated the effect of iron and homocysteine levels on total dispersion of repolarization, in a specific group of subjects.

Cardiac iron deposition predominates in the myocytes rather than interstitium. This condition may disrupt electrical impulse generation and propagation on the myocardial membrane. Iron may increase production of reactive oxygen species and free radicals which may result in the degradation of membrane-associated proteins like ion channels and connexins and also formation of intercardiomyotic fibrosis. Increased intracellular iron is also claimed to distort sodium and potassium channels in addition to formation of oxygen radical.¹⁵ As previously described, by similar mechanism to iron, homocysteine may be arrhythmogenic. Besides, hyperhomocysteinemia is considered to be a surrogate marker of free iron by catalyzing formation of homocysteine from thioethers. However, human studies on the association between homocysteine and iron are very few in number.¹⁶ Our study provided first data about the relation between the novel indices of repolarization, homocysteine, and iron status in a specific group of participants who may have been shown to be associated with rhythm and conduction alterations, morphological changes of the QRS complex and repolarization abnormalities secondary to athletic activities.¹⁷

Our results are compatible with the iron hypothesis and the previous studies suggesting the linear correlation between iron stores and QT dispersion.⁸ However, homocysteine levels were not correlated with neither iron status nor parameters of total dispersion of repolarization. These results may seem conflicting to a certain extent. One possible explanation for our results is that, homocysteine is a surrogate and iron is the main player in the cardiovascular territory. This is also supported with the vitamin B trails that fail to decrease cardiovascular risk despite the decline in the homocysteine levels.¹⁸ Additionally, ferritin may decrease intracellular folate levels which may increase local homocysteine levels without increasing systemic homocysteine levels.¹⁹ On the other hand, athletes are also prone to negative effects of homocysteine and iron metabolisms secondary to increased oxygen demand and muscle activity. Strenuous exercise and overtraining may increase oxidative stress and reactive oxygen species. However, elite athletes may gain resistance to oxidative stress bursts which can also explain the independence of homocysteine to the iron status.²⁰ We advocate that these speculations deserve further investigations.

Additionally, as much as Tp-e interval and Tp-e/QT ratio are of interest, data on their association with cardiac events in healthy individuals are limited, association between QTc and QTc will behave similarly. However, Ulger et al. showed no correlation of QT parameters versus iron and transferrin saturation merit further discussion. It could be expected that Tp-e (QT, QTc, QTd, and cQTd) with both serum ferritin level and liver iron concentration in β -Thalassemia patients.²¹ Contrary to these findings, in an animal model, iron overload was associated with increased QTc interval.²² On the other hand, in our study, which is conducted in a healthy population, transferrin saturation was a weaker predictor of QTc interval.

Study Limitations

Tp-e interval and Tp-e/QT ratio are only surrogate markers of ventricular arrhythmia and these markers are not adequately tested in arrhythmogenesis in structurally normal heart and also elite athletes. Also, we did not evaluate the association between ventricular arrhythmias and Tp-e interval and Tp-e/QT ratio. Transferrin saturation and iron have a diurnal variation and levels may vary on multiple testing. Although these levels may change in inflammatory conditions, none of our study participants had abnormal CRP values which reflect active inflammation.

CONCLUSION

Our study showed that increased transferrin saturation and iron levels were associated with prolonged Tp-e interval and increased Tp-e/QT ratio and these parameters were independent of homocysteine levels in elite athletes.

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