

## The Association between Tp-e interval, Tp-e/QT, and Tp-e/QTc Ratios and Coronary Artery Disease Spectrum and Syntax Score

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### Abstract

**Background:** Coronary artery disease (CAD) causes electrical heterogeneity on ventricular myocardium and ventricular arrhythmia due to myocardial ischemia linked to ventricular repolarization abnormalities.

**Objective:** Our aim is to investigate the impact of increased level of CAD spectrum and severity on ventricular repolarization via Tp-e interval, Tp-e/QT and Tp-e/QTc ratios.

**Methods:** 127 patients with normal coronary artery (group 1), 129 patients with stable CAD (group 2) and 121 patients with acute coronary syndrome (group 3) were enrolled. Tp-e interval, Tp-e/QT and Tp-e/QTc ratios were evaluated as well as baseline demographic and clinical parameters. Kruskal-Wallis one-way ANOVA test was used for comparing quantitative variables with abnormal distribution while One-Way ANOVA test was used for comparing the means between groups with normal distribution. Tukey HSD and Welch tests were used for subgroups analyses with normal distribution. Spearman analysis was used to evaluate the correlation between clinical variables and repolarization markers. A p-value < 0.05 was considered statistically significant.

**Results:** Tp-e interval [66(50-83), 71(59-82) and 76(64-86); group 1,2 and 3 respectively, p<0.001], Tp-e/QT (0.170.02, 0.180.01 and 0.190.01; group 1,2 and 3 respectively, p<0.001) and Tp-e/QTc (0.150.02, 0.160.02 and 0.170.02; group 1,2 and 3 respectively, p<0.001) ratios were found to be associated with increased level of CAD spectrum. Syntax score was positively correlated with Tp-e interval (r=0.514, p<0.001), Tp-e/QT (r=0.407, p<0.001), and Tp-e/QTc ratios (r=0.240, p<0.001).

**Conclusion:** Prolonged Tp-e interval and increased Tp-e/QT and Tp-e/QTc ratios were detected in the presence of CAD and especially in patients with acute ischemic syndromes. (Int J Cardiovasc Sci. 2021; 34(2):179-187)

**Keywords:** Cardiovascular Diseases; Coronary Artery Disease; Arrhythmias Cardiac; Electrocardiography;/ methods; Anthropometry; Score Syntax.

### Introduction

Atherosclerotic cardiovascular diseases are still major underlying reasons for all-cause morbidity and mortality worldwide.<sup>1</sup> While several factors have been described to explain the possible etiologic bases for mortality in the presence of coronary artery disease (CAD), ventricular arrhythmia is one the most important causes of catastrophic

outcomes due to myocardial ischemia.<sup>2</sup> Coronary atherosclerosis can cause electrical heterogeneity in ventricular myocardium and ventricular repolarization abnormalities linked to ventricular arrhythmia. These clinical presentations are seen more commonly in the presence of acute ischemia.<sup>3</sup> While obstructive atherosclerosis damages ventricular myocardium, acute ischemia renders myocardium more sensitive to arrhythmia.

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Electrocardiography (ECG) is often used to detect the electrical instability of the heart. QT intervals and T waves show ventricular depolarization and repolarization on the ECG surface, while abnormalities of the mentioned parameters are important to predict arrhythmias in patients with CAD. The QT interval is described as a continuation from the beginning of the QRS complex to the end of the T wave. Higher QT and corrected QT (QTc) intervals are found to be related to ventricular arrhythmia and mortality, as well as to increased QT dispersion (QTd), which is the difference between the longest and the shortest QT interval.<sup>4-6</sup> The Tp-e interval, which is between the peak and the end of the T wave, is an index of transmural dispersion of repolarization. A prolonged Tp-e interval is related to serious arrhythmias and sudden cardiac death.<sup>7-11</sup> Although QT and Tp-e interval can be affected by heart rates and body weights, the Tp-e/QT ratio is a novel marker to reflect ventricular repolarization and is not affected by changes in heart rates.<sup>12</sup> The present study aimed to investigate the impact of the CAD spectrum on ventricular electrical activity detected by Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios.

## Methods

### Study population

This cross-sectional study was conducted at two tertiary centers from May 2018 to July 2018. One hundred twenty-seven patients with normal coronary arteries (NCA-group 1), one hundred twenty-nine patients with stable coronary artery disease (SCAD-group 2), and one hundred twenty patients with acute coronary syndrome (ACS-group 3) were prospectively and consecutively enrolled in this study.

Patients who had previously undergone coronary angiography and patients with known CAD, severe valvular heart disease, atrial fibrillation, bundle branch block, or evidence of any other intraventricular conduction defect, previous pacemaker implantation, ECGs without clearly analyzable QT interval, electrolyte abnormalities, type I and III antiarrhythmic usages, and end-stage hepatic failure were excluded from the study.

At the beginning of the study, demographic and anthropometric measurements were recorded after performing a detailed cardiovascular and systemic examination. Biochemical analyses including serum creatinine, total cholesterol, low-density lipoprotein (LDL)

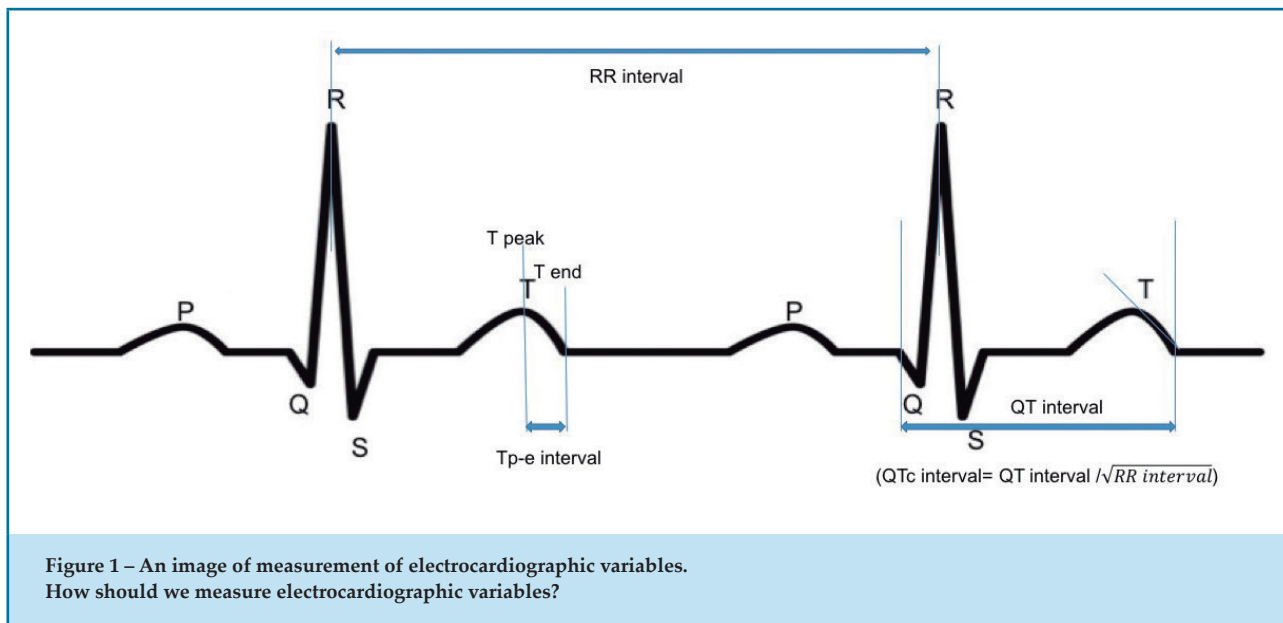
cholesterol, high density lipoprotein (HDL) cholesterol, triglyceride (TG), serum electrolyte levels, and complete blood count were assessed. A 12-lead surface ECG was performed on all subjects before performing coronary angiography. The study was approved by the Ethics Committee of Istanbul Yeni Yuzyil University (Date: 28.05.2018, issue no: 019). Detailed, written, informed consent was obtained from each subject. The study was conducted in accordance with the Declaration of Helsinki.

### Electrocardiography

A 12-lead surface ECG (Nihon Kohden Corporation, Cardiofax M Model ECG-1250, Tokyo, Japan) was performed in the supine position, with a 50 mm/s paper speed and a voltage of 20 mm/s, before performing coronary angiography. While the ECG was performed according to the routine polyclinic evaluation for patients from groups 1 and 2, it was performed in the emergency clinic on patients with ACS. Patients presenting a U wave and biphasic or negative T wave on surface ECG were excluded. Measurements were performed by two different cardiologists who were blinded to the patients' data. Parameters were obtained by using a software after  $\times 400\%$  magnification. The QT interval was measured from the beginning of the QRS complex to the end of the T wave. The QTc interval was calculated by using Bazett's formula ( $QTc \text{ interval} = QT / \sqrt{RR \text{ interval}}$ ).<sup>13</sup> While QTd was measured as the difference between the longest and the shortest QT intervals, QTc dispersion (QTcd) was measured as the difference between the longest and the shortest QTc intervals. Tp-e is measured from the peak of the T wave to the end of the T wave. In accordance with previous studies, the Tp-e was performed from the precordial leads as the preferred lead for measurements of Tp-e intervals in a descending order of V5, V4, V6, and an average value of at least three readings was calculated for each lead and measurement.<sup>14</sup> Finally, Tp-e/QT and Tp-e/QTc ratios were obtained from these measurements (Figure 1).

### CAD categories and severity

Three hundred seventy-six patients were divided into three groups as follows: group 1: patients with NCA, group 2: patients with SCAD, and group 3: patients with ACS according to recent guidelines. Coronary angiography was performed for each patient after hospital admission with chest pain and evidence of ischemia in exercise stress testing in groups 1 and 2. Patients with normal coronary arteries were defined



as group 1. Patients with coronary slow flow were excluded from the study. SCAD is that of a disease causing exercise or stress linked to chest symptoms because of the coronary artery disease with  $\geq 50\%$  stenosis in the left main coronary artery and/or  $\geq 70\%$  stenosis in one or more of the major coronary arteries.<sup>15</sup> These patients were defined as group 2. ACS patients were defined according to the aforementioned criteria. The diagnostic criteria for ST-elevation myocardial infarction (STEMI) were as follows: (a) typical chest pain for more than 20 minutes and (b) ST-segment elevation in at least two contiguous leads with the following cut-off points:  $\geq 0.2\text{mV}$  in men  $\geq 40$  years old;  $\geq 0.25\text{mV}$  in men  $< 40$  years old; or  $\geq 0.15\text{mV}$  in women in leads V2–V3; and/or  $\geq 0.1\text{mV}$  in the other leads. When indicated, posterior (V7–V9) and right (V3R–V4R) derivations were also obtained. A cut-off point was set at  $0.05\text{mV}$  for V7-9 ( $\geq 0.1\text{mV}$  in men  $< 40$  years old) and  $\geq 0.05\text{mV}$  for V<sub>3</sub>R and V<sub>4</sub>R ( $\geq 0.1\text{mV}$  in men  $< 30$  years old). Patients without persistent ( $> 20$  min) ST-segment elevation with acute chest pain and detection of a rise and/or fall of cardiac troponin values with at least one value of above the 99<sup>th</sup> percentile in the upper reference limit was defined as non-ST elevation myocardial infarction (NSTEMI). Both NSTEMI and STEMI patients formed group 3.

The anatomical-based Syntax score was used to evaluate coronary artery disease severity. Briefly, coronary arteries were evaluated as 16 separate segments and segments having 50% or more luminal

stenosis and  $\geq 1.5\text{mm}$  diameter were assessed. Every segment has a pre-specified corresponding weight factor as well as other determining factors, such as calcification and lesion length, which were assessed and taken into account in the Syntax score. The Syntax score calculator ([www.syntaxscore.com](http://www.syntaxscore.com)) was used to obtain each patient's score.

### Statistical analysis

Statistical analysis was made using the computer software Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, IBM Corp., Armonk, New York, USA). Pearson chi-square analysis was performed for categorical variables and Bonferoni method was used for subgroups. Fitness to normal distribution was analyzed with the Kolmogorov-Smirnov test. Data were expressed as "mean $\pm$ standard deviation (SD)" for normal distribution, "median (1<sup>st</sup> and 3<sup>rd</sup> quartiles)" for abnormal distribution and "n (%)" for categorical variables. Kruskal-Wallis one-way ANOVA test was used for comparing quantitative variables without normal distribution while One-Way ANOVA test was used for comparing the means between groups with normal distribution. Tukey HSD and Welch tests were used for subgroup analyses with normal distribution. Spearman analysis was used to evaluate the correlation between clinical variables and repolarization markers. A p-value  $< 0.05$  was considered statistically significant.

## Results

One hundred twenty-seven patients with NCA (group 1), one hundred twenty-nine patients with SCAD (group 2), and one hundred twenty patients with ACS, including seventy-seven NSTEMI and forty-three STEMI patients (group 3) were enrolled in this study. Demographic parameters for each group were demonstrated in Table 1. There were no statistically significant differences in age, gender, smoking status, body mass index, hemoglobin, creatinine, LDL

cholesterol, hypertension, diabetes mellitus, peripheral arterial disease, and use of medication, such as betablocker, angiotensin converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, and statin between three groups. Total cholesterol levels were significantly lower in patients with NCA than other groups and HDL cholesterol levels were significantly higher in group 1. In subgroup analyses, a statistically significant difference was only observed in HDL levels between groups 1 and 3. TG levels were lower in group 1. In subgroup analyses, it was demonstrated that

**Table 1 – Baseline clinical and demographic parameters of study population**

	NCA group (n=127)	SCAD group (n=129)	ACS group (n=120)	P
Age	59 (50-71)	58 (52-67)	57 (48-65)	0.101
Gender (female), n (%)	36.2 (46)	27.1 (35)	30.0 (36)	0.277
Smoking % (n)	45.7 (58)	41.9 (54)	42.5 (51)	0.807
BMI (kg/m <sup>2</sup> )	28 (25-32)	28 (26-29)	28 (27-31)	0.354
Hemoglobin (g/dl)	13.85±1.73	13.6±1.60	13.72±2.03	0.486
Creatinine (mg/dl)	0.80 (0.70-1.00)	0.81 (0.70-1.00)	0.84 (0.70-1.00)	0.206
Total cholesterol (mg/dl)	175 (156-205)	192 (164-223)	188 (164-218)	0.043
LDL cholesterol (mg/dl)	109 (89-128)	114 (89-142)	116 (89-141)	0.228
HDL cholesterol (mg/dl)	44 (38-52)	41 (35-51)	40 (35-46)*	0.011
Triglyceride (mg/dl)	129 (100-165)	146 (106-210) <sup>†</sup>	162 (120-227) <sup>†</sup>	<0.001
HT % (n)	63.8 (81)	58.1 (75)	56.7 (68)	0.481
HL % (n)	18.9 (24)	34.9 <sup>†</sup> (45)	40.8 <sup>†</sup> (49)	0.001
DM % (n)	28.3 (36)	39.5 (51)	32.5 (39)	0.159
PAD % (n)	7.9 (10)	2.3 (3)	9.2 (11)	0.061
Medication				
BB % (n)	41.7 (53)	38.0 (49)	40.8 (49)	0.816
ACEI % (n)	34.6 (44)	39.5 (51)	26.7 (32)	0.097
ARB % (n)	15.7 (20)	8.5 (11)	8.3 (10)	0.099
CCB % (n)	22.8 (29)	32.6 (42)	26.7 (32)	0.213
Statin % (n)	17.3 (22)	21.7 (28)	11.7 (14)	0.108
EF (%)	60 (55-65)	60 (50-60)	55 (45-60) <sup>*</sup>	0.001
Syntax score	0 (0-0)	7 (4-17) <sup>†</sup>	16 (9-23) <sup>††</sup>	<0.001

\* significantly decreased compared to NCA group, <sup>†</sup> significantly increased compared to NCA group, <sup>††</sup> significantly increased compared to SCAD group

(ACEI: angiotensin converting enzyme inhibitor, ACS: acute coronary syndrome, ARB: angiotensin receptor blocker, BB: beta blocker, BMI: body mass index, CCB: calcium channel blocker, DM: diabetes mellitus, EF: ejection fraction, HDL: high density lipoprotein, HL: hyperlipidemia, HT: hypertension, LDL: low density lipoprotein, NCA: normal coronary artery, PAD: peripheral artery disease, SCAD: stable coronary artery disease)

TG levels were lower with a statistically significant difference in group 1 when compared to groups 2 and 3. The prevalence of hyperlipidemia was found to be lower in patients with NCA. Ejection fraction (EF) values were lower in patients with ACS. According to subgroup analyses, statistical significant differences were only found between groups 1 and 3, with lower EF values in group 3 ( $p<0.001$ ).

Electrocardiographic parameters for each group were demonstrated in Table 2. No significant differences were identified in the heart rates among the groups. QRS duration was shorter in group 1 than in the others. However, there was no difference in QRS duration between groups 2 and 3, while groups 2 and 3 presented a statistically significant longer duration time than did

group 1. The QT interval, QTc interval, QTd, QTcd, and Tp-e interval (Figure 2) were prolonged in patients with ACS and shortened in patients with NCA. However, in subgroup analyses, the QTc interval was not found to be different between groups 2 and 3, and QTd was found to be different, with a statistical significance observed only between groups 1 and 3. Tp-e/QT ratio and Tp-e/QTc ratio (Figure 2) were lowest in group 1 and highest in group 3.

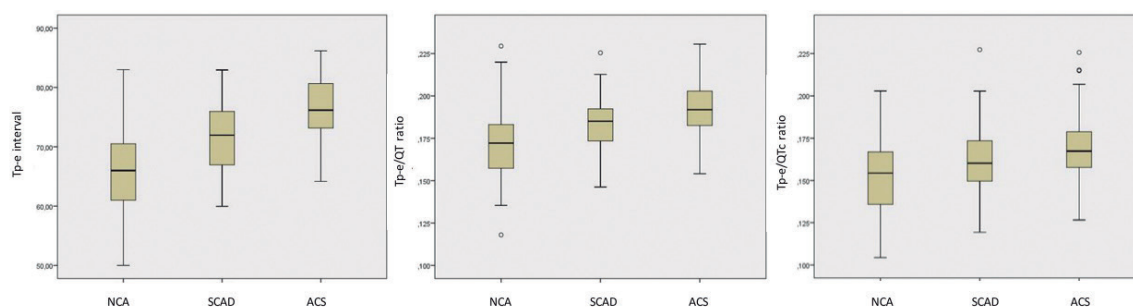
Spearman correlation analyses revealed that there was a negative correlation between LVEF and the Tp-e interval ( $r=-0.103$ ,  $p=0.045$ ), as well as a negative correlation between LVEF and the Tp-e/QT ratio ( $r=-0.106$ ,  $p=0.040$ ) (Figure 3). The syntax score was strongly and positively correlated with the Tp-e interval ( $r=0.514$ ,  $p<0.001$ ), Tp-e/QT ratio ( $r=0.407$ ,  $p<0.001$ ), and Tp-e/QTc ratio ( $r=0.240$ ,  $p<0.001$ ) (Figure 4).

**Table 2 – Comparison of electrocardiographic parameters of the study population**

	NCA group (n=127)	SCAD group (n=129)	ACS group (n=120)	P
Heart rate (beat/min)	79 (68-86)	79 (69-87)	80 (71-88)	0.374
QRS duration (ms)	84±8.8	89±11.1*	87±9.1*	<0.001
QT interval (ms)	381 (372-392)	390 (381-404)*	396 (385-410)*†	<0.001
QTc interval (ms)	432 (406-464)	446 (412-484)*	450 (430-481)*	<0.001
QT dispersion (ms)	35 (32-37)	35 (32-37)	36 (34-38)*	0.026
QTc dispersion (ms)	37.5 (34.5-39.5)	38.0 (34.9-40.0)*	39.25 (37.0-41.7)*†	<0.001
Tp-e interval (ms)	66 (61-71)	71 (66-75)*	76 (73-80)*†	<0.001
Tp-e/QT ratio	0.17±0.02	0.18±0.01*	0.19±0.01*†	<0.001
Tp-e/QTc ratio	0.150.02	0.16±0.02*	0.17±0.02*†	<0.001

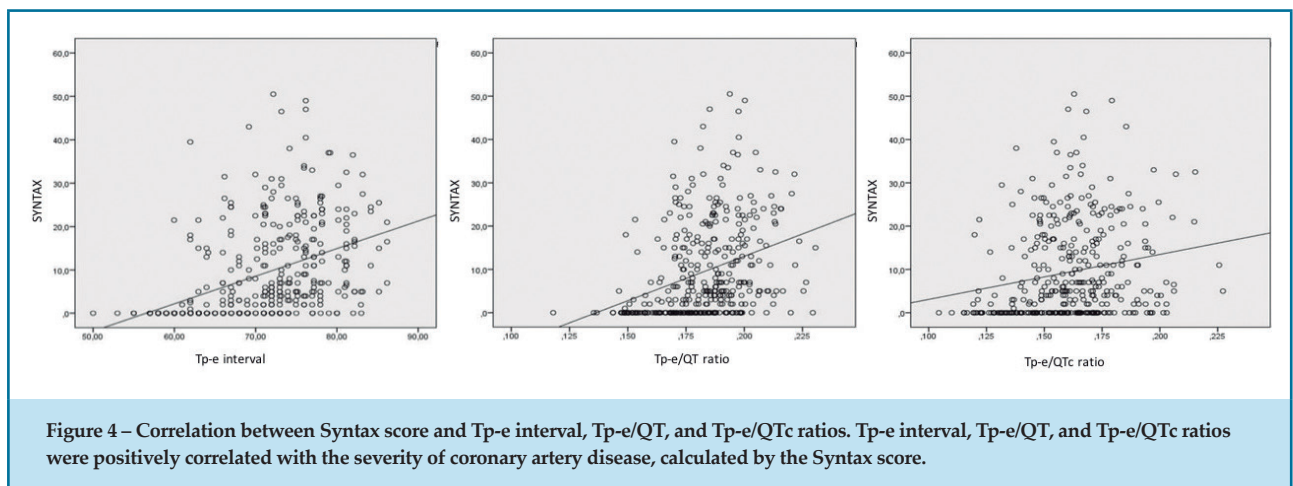
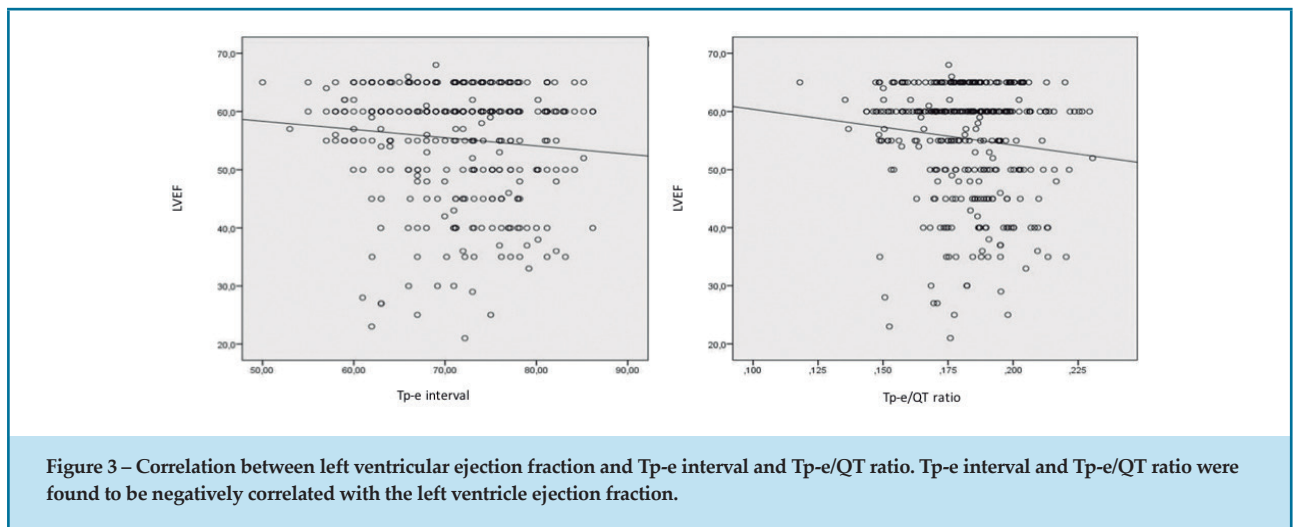
\*significantly increased compared to NCA group, † significantly increased compared to SCAD group

ACS: acute coronary syndrome, NCA: normal coronary artery, SCAD: stable coronary artery disease



**Figure 2 – Comparison of Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios between groups. Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios increase, together with a parallel increase in the severity of coronary artery disease, from normal coronary arteries to an acute coronary syndrome.**





## Discussion

In the present study, the increase in the coronary artery disease spectrum from normal coronary arteries to acute coronary syndrome is accompanied by a parallel prolongation in the Tp-e interval and elongation in the Tp-e/QT and Tp-e/QTc ratios. Additionally, progressive coronary atherosclerosis and unstable disease lead to ventricular repolarization, which seems to be correlated with an increase in the QT interval, QTc interval, QTd, and QTcd. This study also found a negative correlation between LV systolic function and total ventricular dispersion. Coronary artery disease severity is also found to be positively correlated with ventricular repolarization abnormalities if one calculates by Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios.

Obstructive coronary atherosclerosis causes electrical impairment in the ventricle myocardium due to the

imbalance in arterial supply and demand. The size of the ischemic area and the presence of previous scar formation are the main determining factors of myocardial heterogeneity and the formation of arrhythmia. Arrhythmia is related to significant obstructive CAD, leading to ischemic episodes without acute or old myocardial infarction (MI). These pathological pathways result in myocardial electrical imbalance, which is reflected in abnormal ventricular repolarization. While previous studies demonstrated that the incidence of arrhythmia was higher in CAD patients, it was more commonly seen in patients with acute ischemia due to the increased risk of transient ischemic attack with or without previous scar formation. In light of foregoing data, this could be the reason for increased abnormal ventricular repolarization parameters in CAD patients, such as that seen in

groups 2 and 3, than in the control group with normal coronary artery patients. In a study by Pascale et al.,<sup>16</sup> 252 patients who were admitted to the hospital due to ventricular arrhythmia linked to CAD were evaluated, in which acute MI was found to be the most frequent mechanism of arrhythmia. About half of the patients with an acute MI presented a previous MI scar without transient ischemia, whereas the other half presented transient ischemic areas. Patients with obstructive CAD without ACS had a relatively lower risk of arrhythmia than did patients with MI.<sup>16</sup> This supports our results of increased arrhythmia-related ECG findings in group 3 patients as compared to other group patients. Moreover, decreased EF represents the other facilitative factor of ventricular arrhythmia when in the presence of coronary atherosclerosis.<sup>16</sup> Our study also discovered that the EF was significantly lower in patients with ACS. This may well be one of the reasons for prolonged Tp-e intervals and increased Tp-e/QT and Tp-e/QTc ratios due to ischemia-related electrical heterogeneity on the myocardium. Unsurprisingly, these elongated variables could possibly be the predictor of ventricular arrhythmia. Our correlation analyses demonstrated a negative correlation between LVEF and Tp-e and Tp-e/QT ratios. This also supports the negative relationship between LV systolic function and ventricular dispersion of repolarization. In addition to these, patients with left ventricular systolic dysfunction in group 1 may be the reason of abnormal repolarization in the same group when compared to the normal population. Patients with ischemia evidence on exercise stress testing and normal coronary arteries (group 1) may also have impaired ventricular repolarization because of undetected microvascular dysfunction or coronary vasospasm.

According to these data, increased coronary atherosclerosis causes the impairment of left ventricular repolarization. This abnormal repolarization is seen as more distinct in patients with acute coronary events. The syntax score is that of a score showing coronary artery disease severity and is related to adverse cardiac events, such as cardiac arrhythmia. Increased

Tp-e interval and Tp-e/QT and Tp-e/QTc ratios are indicators of abnormal ventricular repolarization and can be related to CAD severity. In this same light, a strong correlation was found between a higher syntax score and an increased Tp-e interval and Tp-e/QT and Tp-e/QTc ratios.

Dyslipidemia is one of the major risk factors for cardiovascular atherosclerotic diseases. While elevated

serum lipid levels are associated with coronary artery disease, they play key roles in atherosclerotic disease spectrum changes from a stable to an unstable disease, such as ACS. In a previous study, it was demonstrated that the presence of CAD and a poorer prognosis of the disease due to acute complication, such as an acute ischemic syndrome, proved to be related to high serum lipid levels.<sup>17</sup> The present study revealed that serum lipid levels, such as total cholesterol and triglyceride, were higher in patients with CAD, especially in ACS patients. Lower HDL levels were also demonstrated in patients with CAD, unveiling another risk factor of coronary atherosclerosis. Although hyperlipidemia did prove to be higher in patients with CAD, serum LDL cholesterol levels exhibited no difference between both groups. This could be explained by the treatment of patients with statin therapy.

Higher QT and QTc intervals are related to an increased risk of mortality due to the occurrence of the early ??? after depolarization. An abnormal depolarization, occurring during phases 2 and/or 3 of the action potential, makes ventricular myocardium sensitive to arrhythmia because of the development of functional reentry.<sup>4,18</sup> Ventricular arrhythmias linked to higher QT and QTc intervals commonly occur in the presence of obstructive coronary atherosclerosis, especially during acute ischemia. One prior study demonstrated that there was a strong positive association between a higher QTc interval and mortality in 3,837 patients with post-myocardial infarction.<sup>19</sup> Moreover, increased QTd, which indicates the dispersion of ventricular repolarization, is commonly related to serious arrhythmia and sudden death.<sup>20</sup> Several studies demonstrated that QTd was a more sensitive marker to detect ventricular arrhythmia, when compared to the QT interval.<sup>21</sup> While QTd tends to increase more in patients with acute MI than in a normal population,<sup>22</sup> Tikiz et al.,<sup>23</sup> revealed that the severity of the localized ischemia was more important than the extent of coronary atherosclerosis.<sup>23</sup> To support these findings, in our study, the QT interval, QTc interval, QTd, and QTcd proved to be increased in patients with obstructive coronary atherosclerosis, and this increase was more distinct in acute coronary syndrome patients. This result is due to the fact that acute ischemia causes ventricular electrical heterogeneity and instability, which often results in ventricular arrhythmia.

Increased dispersion of repolarization is more commonly associated with the heterogeneity of repolarization as compared to the total duration of

repolarization. This degenerated repolarization has proven to be associated with the increased risk of ventricular arrhythmia and sudden cardiac death in various cardiac disorders, especially in patients with CAD.<sup>9-11,14</sup> Coronary atherosclerosis-related clinical conditions are still the most important reasons for cardiac death worldwide. Myocardial ischemia-related ventricular arrhythmias, due to damaged repolarization, are commonly seen in the presence of obstructive CAD. The Tp-e interval, which reflects a transmural dispersion of ventricular repolarization, is related to the increased risk of ventricular arrhythmia and sudden cardiac death in CAD patients.<sup>14</sup> In one study, it was demonstrated that the Tp-e interval was independently associated with cardiac death in patients with obstructive coronary atherosclerosis, while the QTc interval remained normal.<sup>24</sup> The Tp-e interval also proved to be a strong predictor of mortality in STEMI and NSTEMI patients.<sup>11</sup> This can be explained by the increased risk of myocardial injury in the presence of ventricular ischemia, the risk of which is more explicit during acute coronary syndrome. The present study demonstrated that the prolongation of the Tp-e interval was related to CAD, and this prolongation was quite apparent in patients with ACS. This increase could be the predictor of mortality due to the increased risk of ventricular arrhythmia. Tp-e/QT and Tp-e/QTc ratios are novel markers that are more accurate predictors of the dispersion of ventricular repolarization and ventricular arrhythmias than the QT, QTc, and Tp-e intervals. These are also independent predictors of alterations in heart rate and a significant association with ventricular arrhythmia was demonstrated in many clinical conditions.<sup>12</sup> While the higher Tp-e/QT ratio was associated with CAD, in one study, it was demonstrated that the Tp-e/QT ratio was linked to malignant ventricular arrhythmia in patients with STEMI.<sup>25</sup> In the present study, Tp-e/QT and Tp-e/QTc ratios proved to be associated with the CAD spectrum as well as with QT, QTc, and Tp-e intervals. Unsurprisingly, a more distinct increase in ACS patients seemed to be correlated with the increased risk of ventricular arrhythmia and mortality. However, large-scale studies are needed for future investigations.

### Study limitation

The main limitations of the study are the small sample size of the study and the lack of patient follow-up visits concerning ventricular arrhythmia with 24-hour rhythm

monitoring. The other limitation was the lack of data about the information on the actual arrhythmic burden of those patients. Thus, any inference about the actual significance of the modest difference observed in the repolarization parameters as regards the differences in the arrhythmogenic risk among the three study groups remains uncertain. A heterogeneous population of the study was also another limitation, especially considering the fact that NSTEMI and STEMI were evaluated in the same group as ACS patients.

### Conclusions

The presence of myocardial ischemia is one the most important reasons for abnormal ventricular repolarization, which can be reflected on a surface ECG by the Tp-e interval, as well as the Tp-e/QT, and Tp-e/QTc ratios. However, the relationship between the CAD spectrum and repolarization markers has not yet been fully investigated. Unsurprisingly, in the present study, a prolonged Tp-e interval and increased Tp-e/QT and Tp-e/QTc ratios were detected in the presence of CAD as well as in patients with unstable coronary atherosclerosis. These prolongations were seen more distinctly in patients with acute ischemic syndromes. A negative correlation was found between the LV systolic function and the dispersion of the ventricle's myocardium, and a strong and positive correlation was also identified between CAD severity and prolonged Tp-e interval and increased Tp-e/QT and Tp-e/QTc ratios.

### Author contributions

Conception and design of the research: Kahraman S, Dogan A, Kurtoglu N, Erturk M. Acquisition of data: Demirci G, Guler A. Analysis and interpretation of the data: Kahraman S, Dogan A, Demirci G, Guler A, Kalkan AK, Uzun F, Kurtoglu N, Erturk M, Kalkan ME. Statistical analysis: Kahraman S, Dogan A. Writing of the manuscript: Kahraman S, Dogan A, Kalkan AK, Uzun F, Kurtoglu N, Erturk M, Kalkan ME. Critical revision of the manuscript for intellectual content: Kahraman S, Dogan A, Demirci G, Guler A, Kalkan AK, Uzun F, Kurtoglu N, Erturk M, Kalkan ME.

### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.



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There were no external funding sources for this study.

## Study Association

This study is not associated with any thesis or dissertation work.

## Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Yeni Yüzyıl University under the protocol number 019/2018. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

## References

- Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Executive summary: heart disease and stroke statistics—2016 update: a report from the American Heart Association. *Circulation*. 2016;133(4):447-54.
- Wit AL, Janse MJ. Experimental models of ventricular tachycardia and fibrillation caused by ischemia and infarction. *Circulation*. 1992;85(1 Suppl):32-42.
- Zhao X, Xie Z, Chu Y, Yang L, Xu W, Yang X, et al. Association between Tp-e/QT ratio and prognosis in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. *Clin Cardiol*. 2012;35(9):559-64.
- Zhang Y, Post WS, Blasco-Colmenares E, Dalal D, Tomaselli GF, Guallar E. Electrocardiographic QT interval and mortality: a meta-analysis. *Epidemiology*. 2011;22(5):660-70.
- Beinart R, Zhang Y, Lima JA, Bluemke DA, Soliman EZ, Heckbert SR, et al. The QT interval is associated with incident cardiovascular events (the MESA study). *J Am College Cardiol*. 2014;64(20):2111-9.
- Zareba W, Moss AJ, le Cessie S. Dispersion of ventricular repolarization and arrhythmic cardiac death in coronary artery disease. *Am J Cardiol*. 1994;74(6):550-3.
- Kors JA, Ritsema van Eck HJ, van Herpen G. The meaning of the Tp-Te interval and its diagnostic value. *J Electrocardiol*. 2008;41(6):575-80.
- Antzelevitch C, Sicouri S, Di Diego JM, Burashnikov A, Viskin S, Shimizu W, et al. Does Tpeak-Tend provide an index of transmural dispersion of repolarization? *Heart Rhythm*. 2007;4(8):1114-6.
- Castro Hevia J, Antzelevitch C, Tornes Barzaga F, Dorantes Sanchez M, Dorticos Balea F, Zayas Molina R, et al. Tpeak-Tend and Tpeak-Tend dispersion as risk factors for ventricular tachycardia/ventricular fibrillation in patients with the Brugada syndrome. *J Am Coll Cardiol*. 2006;47(9):1828-34.
- Smetana P, Schmidt A, Zabel M, Hnatkova K, Franz M, Huber K, et al. Assessment of repolarization heterogeneity for prediction of mortality in cardiovascular disease: peak to the end of the T wave interval and nondipolar repolarization components. *J Electrocardiol*. 2011;44(3):301-8.
- Erikssen G, Liestol K, Gullestad L, Haugaa KH, Bendz B, Amlie JP. The terminal part of the QT interval (T peak to T end): a predictor of mortality after acute myocardial infarction. *Ann Noninvasive Electrocardiol*. 2012;17(2):85-94.
- Gupta P, Patel C, Patel H, Narayanaswamy S, Malhotra B, Green JT, et al. T(p-e)/QT ratio as an index of arrhythmogenesis. *J Electrocardiol*. 2008;41(6):567-74.
- Goldenberg I, Moss AJ, Zareba W. QT interval: how to measure it and what is "normal". *J Cardiovasc Electrophysiol*. 2006;17(3):333-6.
- Haarmark C, Hansen PR, Vedel-Larsen E, Pedersen SH, Graff C, Andersen MP, et al. The prognostic value of the Tpeak-Tend interval in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. *J Electrocardiol*. 2009;42(6):555-60.
- Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013;34(38):2949-3003.
- Pascale P, Schlaepfer J, Oddo M, Schaller MD, Vogt P, Fromer M. Ventricular arrhythmia in coronary artery disease: limits of a risk stratification strategy on the ejection fraction alone and impact on infarct localization. *Europace*. 2009;11(12):1639-46.
- Pekkanen J, Linn S, Heiss G, Suchindran CM, Leon A, Rifkind BM, et al. Ten-year mortality from cardiovascular disease in relation to cholesterol level among men with and without preexisting cardiovascular disease. *N Eng J Med*. 1990;322(24):1700-7.
- Antzelevitch C, Shimizu W, Yan GX, Sicouri S. Cellular basis for QT dispersion. *J Electrocardiol*. 1998;30(Suppl):168-75.
- Peters RW, Byington RP, Barker A, Yusuf S. Prognostic value of prolonged ventricular repolarization following myocardial infarction: the BHAT experience. *J Clin Epidemiol*. 1990;43(2):167-72.
- Dilaveris PE, Gialafos EJ, Sideris SK, Theopistou AM, Andrikopoulos GK, Kyriakidis M, et al. Simple electrocardiographic markers for the prediction of paroxysmal idiopathic atrial fibrillation. *Am Heart J*. 1998;135(5 Pt 1):733-8.
- Kautzner J, Malik M. QT interval dispersion and its clinical utility. *Pacing Clin Electrophysiol*. 1997;20(10 Pt 2):2625-40.
- Glancy JM, Garrat CJ, de Bono DP. Dynamics of QT dispersion during myocardial infarction and ischemia. *Int J Cardiol*. 1996;57(1):55-60.
- Tikiz H, Terzi T, Balbay Y, Demir AD, Soylu M, Keles T, et al. QT dispersion in single coronary artery disease: is there a relation between QT dispersion and diseased coronary artery or lesion localization? *Angiology*. 2001;52(1):43-51.
- Panikkath R, Reinier K, Uy-Evanado A, Teodorescu C, Hattenhauer J, Mariani R, et al. Prolonged Tpeak-Tend interval on the resting ECG is associated with increased risk of sudden cardiac death. *Circ Arrhythm Electrophysiol*. 2011;4(4):441-7.
- Shu J, Li H, Yan G, Cui C. Tp-e/QT ratio as a predictive index of sudden cardiac death in patients with ST-segment elevation myocardial infarction. *J Xi'an Jiaotong Univ Med Sci*. 2010;31:441-3.

