Association of Tp-e/QT ratio with SYNTAX score II in patients with coronary artery disease

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\textbf{ABSTRACT}

Background. The SYNTAX score II (SS) is an angiographic tool, which grades the complexity of coronary artery lesions and predicts short- and long-term events. Tp-e/QT ratio is a novel electrocardiographic marker for the risk of ventricular arrhythmias. We aimed to investigate whether there was a correlation between SS and Tp-e/QT ratio.

Methods. A total of 227 consecutive patients who underwent elective coronary angiography were enrolled in this study. Patients who had a lumen diameter \(>1.5\) mm and at least \%50 diameter stenosis on coronary angiogram were determined as coronary artery disease (CAD) group, and others were identified as a control group. The SS was calculated for the CAD group, and SS \(\geq 23\) was defined as a high SS group, and SS \(< 23\) was identified as a low SS group.

Electrocardiographic indices, such as Tp-e and Tp-e/QT, were measured for all patients. A multivariable logistic regression analysis was performed with variables age, interventricular septum thickness (IVS), hypertension, and Tp-e/QT. Results. Tp-e interval and Tp-e/QT ratio were higher in the CAD group compared with the control group. Tp-e, corrected Tp-e (cTP-e) and Tp-e/QT ratio were similar between SS group than in the low SS group. The cTP-e and Tp-e/QT were correlated with SS score. Age, IVS and Tp-e/QT ratio were independent predictors of high SS in the logistic regression analysis.

Conclusions. Tp-e/QT ratio was an independent predictor of high SS and might be used for risk stratification in CAD patients.

\textbf{Introduction}

Coronary artery disease (CAD) is defined as a pathological process characterized by atherosclerotic plaque aggregation in the coronary arteries. CAD is a significant mortality and morbidity cause worldwide. Because of the prognostic significance, the severity of coronary artery occlusion was assessed by many scoring systems, two of which are SYNTAX score II (SS) and Gensini scores that are widely used [1]. The SS was calculated according to the location, number, and complexity of lesions in the coronary arteries on the coronary angiogram [2]. SS not only detects the severity of the coronary lesion but also predicts in-hospital and long-term outcomes [3].

Life-threatening arrhythmias due to coronary artery occlusion are the most common cause of sudden cardiac death in CAD patients. Spatial dispersion of repolarization indicates heterogeneity of repolarization, which is known to be a causative risk of proarhythmia [4]. Several electrocardiographic indexes, such as QT dispersion, QT interval, QTc interval, and T wave micro alternans, can be used for the quantification of the dispersion of repolarization (TDR) [5]. Also, several studies have demonstrated that Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio can be used for the evaluation of ventricular repolarization and are useful for establishing ventricular arrhythmic risk [6–8]. Furthermore, compared with a traditional and older index, QT dispersion, novel indexes including Tp-e and Tp-e/QT ratio were found to be more susceptible to state arrhythmias [9].

In this study, we aimed to investigate whether there is a correlation between SYNTAX score II and Tp-e/QT interval for detecting high-risk patients.

\textbf{Methods}

This study included 227 consecutive individuals who underwent elective coronary angiography with suspected coronary artery stenosis between July 2018 and July 2019. Patients aged between 20 and 85 years with a positive treadmill-exercise test, myocardial perfusion scintigraphy, or with stable angina pectoris were admitted to this study. Standard coronary angiography was performed through the femoral or radial artery using the Judkins technique. Four angiographic images for the left coronary artery and two angiographic images for the right coronary artery were obtained from all patients. The coronary angiograms were evaluated by two independent, experienced interventional cardiologists.
who were blinded to the patients’ data. In case of disagreement, the decision of the third cardiologist was required and the final decision was reached after the joint agreement. The CAD group was determined according to the coronary artery lesion with a lumen diameter $>1.5$ mm and at least 50% diameter stenosis. Patients with $<50\%$ diameter stenosis of the coronary lesion were included in the control group. After this discrimination, 120 patients were classified as CAD group (54% male; mean age 59 $\pm$ 11 years), and 107 patients without CAD as the control group (48% male; mean age 57 $\pm$ 10 years). The SS was calculated using the online SS calculator 2.10 (www.syntaxscore.com) in all patients in the CAD group. Based on the SYNTAX score II, patients in the CAD group were divided into two groups high ($\geq 23$) and low (<23) SS group. All clinical and demographic characteristics, comorbidities [hypertension (HT), diabetes mellitus (DM), dyslipidemia, and smoking status] and family history of CAD, laboratory values, electrocardiographic (ECG) recordings, and ECG parameters were obtained from hospital recordings. The Local Ethics Committee of our institute approved the study of our institute.

ECG recordings, at a speed of 25 mm/s and voltage of 10 mm/mV, were determined by two independent, experienced cardiologists who were blinded to all patients’ data. All ECGs were scanned and loaded on a computer and evaluated with a digital software java application (imagej.nih.gov/ij/) regarding ECG indexes such as heart rate, Tp-e interval [the interval from the peak- to end-of Twave, in milliseconds (ms)], cTp-e [correction of Tp-e interval for heart rate using the formula; (Tp-e interval $/H_2$O881R-R)], QT interval [from the beginning of the QRS complex to the end of the T wave, in milliseconds (ms)], QTc (correction of QT interval for heart rate with Bazett’s formula), Tp-e/QT, and Tp-e/QTc ratio for analyzing efficiently. All measurements were obtained from all six precordial leads and were the mean value of three consecutive beats of each lead, and the value recorded was the maximum value.

**Exclusion criteria were as follows**

Previous history of myocardial infarction, moderate or severe valvular heart disease, history of ventricular arrhythmias, prior pacemaker implantation, bundle branch block or evidence of any other intraventricular conduction defects, serious illnesses, history of atrial fibrillation, cardiomyopathy, abnormal thyroid function test, abnormal electrolyte values or usage of antiarrhythmic drugs that are possible to influence the QT interval, and patients without a noticeably analyzable ECGs.

Statistical analyses were calculated using R-software v. 3.6.3 (R statistical software, Institute for Statistics and Mathematics, Vienna, Austria). For testing the distribution of normality, the Kolmogorov–Smirnov test was used. Quantitative variables with a normal distribution were represented as arithmetical mean $\pm$ standard deviation, whereas those without a normal distribution were represented as the median ($25^{th}$–75th interquartile range). Categorical variables were denoted as numbers and %. The Student’s t-test was used to compare normally distributed variables and the Mann–Whitney U test for non-normally distribution. The Chi-square test or Fisher’s exact test was used to compare categorical variables, as appropriate. Spearman’s rank correlation analysis was used for the detection of correlations between variables. For determining independent predictors of the high SS group in the CAD group, univariable logistic regression analysis was used, and those that showed significant association with high SS were included in multivariable analysis, including age, the presence of hypertension, IVS, and Tp-e/QT. Receiver operating characteristic (ROC) curve analyses were performed to establish the best cut-off value of Tp-e and Tp-e/QT for detecting a high SS score. Lin’s concordance correlation coefficient was calculated for intra- and interobserver variabilities in Tp-e and QT measurements. Intra- and interobserver concordance correlation coefficients were 0.992 (95% CI, 0.989–0.994) and 0.991 (95% CI, 0.987–0.993) for Tp-e, and 0.991 (95% CI, 0.988–0.993) and 0.987 (95% CI, 0.985–0.990) for QT, respectively. A two-tailed $p$-value of <.05 was considered to be statistically significant.

**Results**

In this study, we included 120 consecutive patients with coronary artery disease [65 males (58%); mean age 59 $\pm$ 11 years] and 107 patients with normal coronary arteries [51 males (47.7%); mean age, 57 $\pm$ 9 years]. Patients with CAD had higher creatinine levels, higher interventricular septum diameters (IVS), lower left ventricular ejection fraction (LVEF), and lower heart rates when compared with the control group. ECG indexes, such as Tp-e ($p < .001$), cTp-e ($p < .001$), QT ($p = .001$), Tp-e/QT ratio ($p < .001$), and Tp-e/QTc ratio ($p < .001$), were higher in the CAD group than in the control group. Other baseline characteristics, clinical, and laboratory findings of all patients are given in Table 1.

Table 2 demonstrates the comparisons of basal demographic, laboratory, and ECG parameters between patients with high and low SS in the CAD group ($n = 120$) of the study population. The high SS group was older, had a higher incidence of HT, and had higher IVS diameters compared with the low SS group. Tp-e ($p = .02$), cTp-e ($p = .002$), Tp-e/QT ($p = .005$) and Tp-e/QTc ($0.017$) were higher in high SS group than in low SS group. cTp-e interval and Tp-e/QT ratio were significantly correlated with SS in CAD group patients (correlation coefficient:0.29; 0.23, $p$-value:.001; .011), respectively (Figures 1 and 2). Univariable and multivariable logistic regression analyses were calculated for detecting independent predictors of high SS in patients with CAD. Univariate analysis showed that age, HT, IVS, and Tp-e/QT ratio were the independent predictors of high SS in CAD patients (Table 3). The cut-off values of Tp-e interval and Tp-e/QT ratio for predicting high SS in the CAD group were 103.2 with a sensitivity of 66%
and specificity of 52.9% [AUC, 0.624; 95% CI (0.523–0.726), p = .013] and 0.227 with a sensitivity of 72% and specificity of 41.4% [AUC, 0.633; 95% CI (0.532–0.734), p = .009], respectively (Figure 3).

**Discussion**

The results of our study demonstrated that Tp-e interval, QT duration, Tp-e/QT ratio, and Tp-e/QTc ratio were considerably higher in patients with CAD compared with patients with normal coronary arteries. Furthermore, Tp-e, Tp-e/QT ratio, and Tp-e/QTc ratio were higher in the high SS group than in the low SS group, and Tp-e/QT was an independent predictor of high SS in patients with CAD.

Despite early detection with imaging modalities and considerable improvements in treatment, atherosclerotic cardiovascular disease remains the leading cause of morbidity and mortality worldwide [10]. Ventricular arrhythmias (VAs), which include a variety from the premature ventricular complex (PVC) to ventricular fibrillation (VF), have a clinical spectrum that ranges from asymptomatic to cardiac arrest [11]. Most life-threatening VAs are associated with ischemic heart disease, particularly in older patients [11]. Furthermore, VAs are correlated with the severity of ischemic heart disease, particularly in older patients [11].

**Table 1.** Comparison of demographical, clinical, and electrocardiographic parameters of patients with coronary artery disease and normal coronary artery.

| Variables                  | Normal coronary artery group (n = 107) | Coronary artery disease group (n = 120) | p Value |
|----------------------------|---------------------------------------|----------------------------------------|--------|
| Age, years                 | 57 ± 10                               | 59 ± 11                                | .09    |
| Gender (male), n (%)       | 51 (48)                               | 65 (54)                                | .33    |
| BMI (kg/m²)                | 22.8 (21–24.8)                        | 23.3 (21.4–25.6)                       | .28    |
| Smoking, n (%)             | 50 (47)                               | 71 (59)                                | .06    |
| Hypertension, n (%)        | 38 (36)                               | 50 (42)                                | .34    |
| DM, n (%)                  | 18 (17)                               | 26 (22)                                | .36    |
| Dyslipidemia, n (%)        | 14 (13)                               | 20 (17)                                | .45    |
| Family history, n (%)      | 22 (21)                               | 28 (23)                                | .62    |
| WBC (x10⁹/L)               | 7.1 ± 1.6                             | 7.4 ± 1.4                              | .11    |
| Creatinine (mmol/L)        | 0.05 (0.04–0.06)                      | 0.05 (0.04–0.06)                       | .03    |
| eGFR, mL/min/1.73m²        | 151 (123–183)                         | 149 (118–188)                          | .64    |
| Sodium (mmol/L)            | 7.8 ± 0.16                            | 7.8 ± 0.20                             | .07    |
| Potassium (mmol/L)         | 0.23 (0.21–0.26)                      | 0.23 (0.22–0.25)                       | .81    |
| Calcium (mmol/L)           | 0.5 (0.49–0.52)                       | 0.51 (0.49–0.52)                       | .32    |
| Magnesium (mmol/L)         | 0.12 (0.11–0.13)                      | 0.12 (0.11–0.13)                       | .12    |
| LVEF (%)                   | 60 (55–60)                            | 50 (40–50)                             | <.001  |
| IVS (mm)                   | 11 (11–12)                            | 12 (12–13)                             | <.001  |
| LV mass (g)                | 103 (93–193)                          | 100 (80–222)                           | .12    |
| Heart rate (beats/min)     | 74 ± 15                               | 70 ± 13                                | .03    |
| Tp-e (ms)                  | 80 (70–90)                            | 100 (80–110)                           | <.001  |
| Tp-e/QT ratio              | 0.21 ± 0.17                           | 0.25 ± 0.05                            | <.001  |
| Tp-e/QTc ratio             | 0.19 ± 0.04                           | 0.23 ± 0.04                            | <.001  |

BMI: body mass index; WBC: white blood cell; RDW: red cell distribution width; MPV: mean platelet volume; LVEF: left ventricular ejection fraction; IVS: interventricular septum; LV: left ventricle; Tp-e: the interval from the peak- to end- of T wave; QTc: correction of QT interval for heart rate with Bazett’s formula.

**Table 2.** Comparison of demographical, clinical, and electrocardiographic parameters between low and high SYNTAX score groups.

| Variables                  | Low SYNTAX score group (n = 70) | High SYNTAX score group (n = 50) | p Value |
|----------------------------|---------------------------------|----------------------------------|--------|
| Age, years                 | 57 ± 9                          | 62 ± 12                          | .03    |
| Gender (male), n (%)       | 36 (51)                         | 29 (58)                          | .48    |
| BMI (kg/m²)                | 23.8 ± 3.2                      | 23.4 ± 3.1                       | .43    |
| Smoking, n (%)             | 40 (57)                         | 31 (62)                          | .59    |
| Hypertension, n (%)        | 21 (30)                         | 29 (58)                          | .002   |
| Dyslipidemia, n (%)        | 9 (12.9)                        | 11 (22)                          | .19    |
| DM, n (%)                  | 14 (20)                         | 12 (24)                          | .6     |
| RDW (%)                    | 13.1 (12.5–13.5)                | 13.2 (12.5–14.3)                 | .202   |
| MPV (%)                    | 10.2 (9.6–10.8)                 | 10.6 (9.5–11.3)                  | .32    |
| Tp-e/QT ratio              | 0.24 ± 0.05                     | 0.26 ± 0.04                      | <.001  |
| Tp-e/QTc ratio             | 0.22 ± 0.04                     | 0.24 ± 0.04                      | <.001  |

BMI: body mass index; DM: diabetes mellitus; RDW: red cell distribution width; MPV: mean platelet volume; LVEF: left ventricular ejection fraction; QTc: correction of QT interval for heart rate; QT: the interval from the beginning of the QRS complex to the end of the T wave; Tp-e: correction of Tp-e interval for heart rate; QTc: correction of QT interval for heart rate with Bazett’s formula.

**Figure 1.** Correlation of SYNTAX score with Tp-e/QT ratio.

**Figure 2.** Correlation of SYNTAX score with Tp-e interval.
coronary artery lesions, and also patients with high SS have more frequent arrhythmic events [12].

The dispersion of repolarization produces voltage gradients, which lead to life-threatening arrhythmias [13]. Tp-e interval, the interval between the peak and the end of the T wave, was established as a valuable index of arrhythmic events, which reflects spatial dispersion of ventricular repolarization [14,15]. The peak of the T wave represents the repolarization of epicardial cells, whereas the end of the T wave represents the repolarization of M cells; thus Tp-e interval demonstrates total (transmural, apicobasal, and global) TDR [16]. Recently, Tp-e/QT ratio has been committed as a more definitive measure of the TDR compared with QTd, cQTd, and Tp-e intervals in several studies. Furthermore, the Tp-e/QT ratio is accepted to be robust to alterations in heart rate because dynamic changes dependent on heart rate occur with a similar proportion in QT and Tp-e interval, concomitantly [15]. Tp-e/QT ratio has been studied in a variety of diseases, including coronary artery ectasia, slow coronary flow, sarcoidosis, psoriasis, obstructive sleep apnea, and ST-segment elevation myocardial infarction [17–23]. Kasapkara et al. showed an increased Tp-e/QT ratio in sarcoidosis hearts [24]. A prospective study conducted among hypertrophic cardiomyopathic patients revealed that Tp-e/QT ratio was an independent predictor of ventricular arrhythmia in those patients [18]. The relation of the Tp-e/QT ratio with coronary artery diseases has been investigated in some studies. Patients with the slow coronary flow and coronary ectasia had a higher Tp-e/QT ratio relative to patients with normal coronary arteries [19,22]. Duyuler et al. showed that Tp-e and Tp-e/QT ratio significantly shortened after successful myocardial reperfusion, which was assessed by myocardial blush grade, and this shortness was correlated with blush grade in patients with ST-segment elevated myocardial infarction (STEMI) [23]. Çağdaş et al. reported similar findings in which the Tp-e interval was significantly correlated with reperfusion success and was an independent predictor of failed ST-segment resolution [25]. In another study, the Tp-e/QT ratio was found to be an independent predictor of all-cause death and cardiac death in STEMI and was correlated with both short- and long-term outcomes [26]. Wang et al. demonstrated that the Tp-e/QT ratio was prolonged during STEMI in patients with vasospastic angina who had arrhythmic events and turned to normal with the resolution of ST-segment elevation compared with patients with free of arrhythmia [27].

Myocardial ischemia due to coronary artery occlusion contributes to electrochemical and metabolic alterations in ventricular muscles, which have an effect on tissue oxygenation, ion channel functions, electrochemical gradient, and pH. Because these changes affect the duration of action potentials, the Tp-e interval prolongs, and Tp-e/QT becomes greater. They might reasonably be expected to be relevant to the degree of ischemia, which is correlated with the grade and extent of coronary artery occlusion [26,28,29]. From this point, prolongation of the Tp-e interval and the Tp-e/QT ratio could be predictors for high SS. It is recognized that myocardial ischemia induces QT time prolongation [30]. Although the high SS group in our study had numerically greater values of QT and QTc than the control group, there were no statistically

Table 3. Independent predictors of high SYNTAX score with univariate and multivariate p-value, OR with 95% CI.

| Variables          | Univariate OR, (95% CI) | p Value | Multivariate OR, (95% CI) | p Value |
|--------------------|-------------------------|---------|---------------------------|---------|
| Gender (male)      | 1.304 (0.628–2.710)    | .46     |                           |         |
| BMI                | 0.953 (0.845–1.074)    | .43     |                           |         |
| Age                | 1.040 (1.003–1.079)    | .03*    | 1.053 (1.008–1.100)       | .02     |
| Hypertension       | 0.310 (0.145–0.663)    | .003*   | 0.846 (0.336–2.132)       | .72     |
| IVS                | 2.124 (1.463–3.081)    | <.001*  | 2.233 (1.445–3.453)       | <.001   |
| MPV                | 1.102 (0.741–1.639)    | .63     |                           |         |
| RDW                | 1.295 (0.968–1.732)    | .08     |                           |         |
| Heart rate         | 1.008 (0.980–1.036)    | .58     |                           |         |
| Tp-e/QT            | 1.127 (1.033–1.229)    | <.001*  | 1.179 (1.064–1.306)       | .002    |

BMI: body mass index; IVS: interventricular septum; MPV: mean platelet volume; RDW: red cell distribution width; Tp-e: the interval from the peak to the end of T wave; QT: the interval from the beginning of the QRS complex to the end of the T wave.

*Variables showed a marginal association with high-SYNTAX score group included multivariable regression model.

Figure 3. ROC (Receiver operating characteristic) curves of Tp-e interval and Tp-e/QT ratio for detecting high SYNTAX score.
significant differences between the groups. Ciobanu et al. demonstrated that age was positively correlated with QT and negatively correlated with Tp-e in lead V1. Thus, the Tp-e/QT ratio is expected to be lower with older age. In our study, the high SS group had a higher Tp-e/QT ratio despite the older age than the low SS group. In past studies, it was demonstrated that HT and left ventricular hypertrophy were associated with higher values of Tp-e/QT [31–33]. The high SS group of our study had more frequent HT and greater IVS diameters than the control group. In multivariable regression analysis, despite these cofounders such as age, IVS and HT, the Tp-e/QT ratio remained significantly correlated with high SS.

Our study showed that both Tp-e and Tp-e/QT had discriminative abilities for the classification of patients with high and low SS scores in CAD group as demonstrated by ROC curves. In spite of the AUC values of Tp-e and Tp-e/QT being significantly different from the reference line in ROC curve analysis, the values of AUC were relatively lower than the generally acceptable value (AUC = 0.70). In addition, the Tp-e and Tp-e/QT had relatively higher sensitivities but lower specificities for detecting high SS. Thus, it should be kept in mind that the negative predictive values of Tp-e and Tp-e/QT were lower when compared with positive predictive values in detecting high SS. However, in terms of the clinical decision, it is more important to diagnose high SS than low SS. So, these cut-off values might be useful in detecting high SS but not excluding low SS. Finally, the ROC curve is a non-parametric demonstration of current data and cannot be generalized to the all population. Thus, it is suggested that the results of regression analysis are more powerful and had strong evidence than a ROC curve for predicting a dependent variable. The Tp-e and Tp-e/QT were independently associated with high SS as detected in logistic regression analysis in this study. There was a relatively poor correlation between Tp-e, Tp-e/QT, and SYNTAX score II (r = 0.29, r = 0.23) but with statistical significance (p < .05 for both). Finally, with correlation and logistic regression analysis results, it can be concluded that the Tp-e/QT is significantly associated with a high SYNTAX score II in this study.

Our research might have important clinical implications. The anticipation of high SS in CAD patients can be crucial in determining high-risk groups. Based on our findings, Tp-e and Tp-e/QT may be employed as simple and easy-to-calculate ECG measures for recognizing high-risk individuals with significant coronary artery lesions. This ECG measure might also be utilized to stratify individuals with existing CAD for future arrhythmic episodes. Finally, we consider that our findings may help to elucidate the pathophysiological reasons underlying the higher occurrence of ventricular arrhythmias by revealing an increase in ventricular repolarization heterogeneity in individuals with severe CAD.

Limitations
The retrospective study design and the small sample size were the major limitations of this study. There were several exclusion criteria, which unfortunately decrease the usefulness of the findings in everyday practice and a bigger population. We used anatomical calculation of coronary artery disease severity with SYNTAX score II in this study. The more precise calculation could be done by using functional Syntax Score and FFR measurements of the border-line lesion, which could be an idea for further research. Prospective studies may give more detailed information about the relation of the severity of coronary artery stenosis with Tp-e/QT in terms of arrhythmic events, morbidity, and mortality. So, further prospective studies with larger sample sizes are needed to be done.

Conclusion
This study identified that the Tp-e interval and Tp-e/QT ratio, which are considered as new indices of arrhythmia, were higher in patients with CAD compared with patients with normal coronary arteries. The Tp-e interval and Tp-e/QT ratio were also independent predictors of high SS in patients with detectable CAD. In conclusion, the Tp-e interval and Tp-e/QT ratio prolonged and were positively correlated with the extent and severity of CAD, indicating that patients with high SS might have greater heterogeneity of repolarization, which may predispose them to life-threatening arrhythmias.

Author contributions
Concept/design: F.Ş., M.S., T.Ç., T.A.; Data analysis/interpretation: F.Ş.; Drafting article: F.Ş., M.S., T.Ç.; Critical revision of article: F.Ş., M.S., T.Ç.; Approval of article: F.Ş., M.S., T.Ç., T.A.; Statistics: F.Ş.; Funding secured by: M.S.; Data collection: F.Ş., M.S., T.A.

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