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Tp-Te Interval and Tp-Te/QT Ratio Predict Coronary Artery Disease Severity in Non-ST Segment Elevation Acute Myocardial Infarction

Tp-Te Aralığı ve Tp-Te/QT Oranı, ST Yükselmesiz Akut Miyokard Enfarktüsünde Koroner Arter Hastalığı Şiddetini Öngörmektedir

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ABSTRACT

Objective: Novel electrocardiographic parameters such as Tp-Te interval and Tp-Te/QT ratio have been recently found to be associated with ischemia, and these markers' potential of predicting ventricular arrhythmias and mortality has been demonstrated in last decade. In this study, we aimed to investigate the relationship between the coronary artery disease severity and the Tp-Te interval, Tp-Te/QT, QT, and corrected QT interval in patients with non-ST segment elevation myocardial infarction (NSTEMI).

Methods: In this retrospective, single center cohort study we included 241 patients with NSTEMI. The recorded electrocardiograms (ECGs) and coronary angiograms were reviewed, and patients' demographics, laboratory values, ECG parameters, and the Syntax score (SS) were compared. The study population was divided into the following two groups: low SS (SS <22, n=158) and high SS (SS ≥22, n=83).

Results: The Tp-Te interval [79.2 (±12.2) ms vs. 111.6 (±11.5) ms, p<0.001], cTp-Te [87.7 (±14.5) ms vs. 116.6 (±15.8) ms, p<0.001], and Tp-Te/QT [0.210 (0.029) vs. 0.243 (0.028), p<0.001] were statistically significantly higher in the high SS group compared to the low SS group. In the multivariate regression analysis, the Tp-Te interval [odds ratio (OR): 1.464, confidence interval (CI): 1.118-1.918; p=0.006] and Tp-Te/QT ratio (OR: 0.210, CI: 0.215-0.562; p<0.001) were found to be the independent predictors of a high SS score. Tp-Te (rho =0.504, p<0.001) and Tp-Te/QT (rho =0.512, p<0.001) ratios were positively correlated with the SS.

Conclusion: This study demonstrates that prolonged Tp-Te interval and increased Tp-Te/QT ratio are independent predictors of high SS in patients with NSTEMI.

Keywords: Coronary artery disease severity, Tp-Te and Tp-Te/QT, novel ECG index, repolarisation parameters

ÖZ

Amaç: Tp-Te aralığı ve Tp-Te/QT oranı gibi yeni elektrokardiyografik parametrelerin iskemi ile ilişkili olduğu yakın zamanda bulunmuş ve bu belirteçlerin ventriküler aritmileri ve mortaliteyi öngörme potansiyeli son on yılda gösterilmiştir. Bu çalışmada, ST yükselmesiz miyokard enfarktüslü (STYsizME) hastalarda koroner arter hastalığı ciddiyeti ile Tp-Te intervali, Tp-Te/QT, QT ve düzeltilmiş QT arasındaki ilişkiyi araştırmayı amaçladık.

Yöntemler: Bu retrospektif, tek merkezli kohort çalışmasına 241 STYsizME hastasını dahil ettik. Kaydedilen elektrokardiyogramlar (EKG) ve koroner anjiyogramlar gözden geçirildi ve hastaların demografik özellikleri, laboratuvar değerleri, EKG parametreleri ve Syntax skoru (SS) karşılaştırıldı. Çalışma popülasyonu şu iki gruba ayrıldı: Düşük SS (SS <22, n=158) ve yüksek SS (SS ≥22, n=83).

Bulgular: Tp-Te aralığı [79,2 (±12,2) ms vs. 111,6 (±11,5) ms, p<0,001], cTp-Te [87,7 (±14,5) ms ile 116,6 (±15,8) ms, p<0,001] ve Tp-Te/QT [0,210 (0,029) ve 0,243 (0,028), p<0,001] düşük SS grubuna kıyasla yüksek SS grubunda istatistiksel olarak anlamlı derecede yüksekti. Çok değişkenli regresyon analizinde Tp-Te aralığı [olasılık oranı (OO): 1,464, güven aralığı (GA): 1,118-1,918; p=0,006] ve Tp-Te/QT oranı (OO: 0,210, GA: 0,215-0,562; p<0,001),

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yüksek SS puanının bağımsız öngörücüleri olarak bulundu. Tp-Te (rho =0,504, p<0,001) ve Tp-Te/QT (rho =0,512, p<0,001) oranları SS ile pozitif korelasyon gösterdi.

Sonuç: Bu çalışma, uzamış Tp-Te aralığı ve artan Tp-Te/QT oranının STYsizME hastalarında yüksek SS'nin bağımsız öngörücüleri olduğunu göstermektedir.

Anahtar kelimeler: Koroner arter hastalığı şiddeti, Tp-Te ve Tp-Te/QT, yeni EKG indeksi, repolarizasyon parametreleri

INTRODUCTION

Non-ST segment elevation myocardial infarction (NSTEMI) is an important cause of morbidity and mortality. Patients may present with transient chest pain as well as severe conditions such as malignant arrhythmia, syncope, and cardiac arrest. The severity of coronary artery disease (CAD), which has an important place in diffuse ischemia and necrosis, also plays a determinant role in the awareness of clinical progression (1). Diffuse and complex vessel involvement may be seen in daily clinical interventions for patients with NSTEMI. The Syntax score (SS), which has angiographic and clinical value, is currently used to make decisions about CAD severity and diffusiveness, possible complications, and long-term patient clinical outcome (2,3).

The Tp-Te interval is obtained from an electrocardiogram (ECG) by measuring the duration between the peak and termination of the T wave (4). QT and QTc reflect ventricular depolarization and repolarization, while Tp-Te has been proposed as a measure of transmural dispersion of repolarization (5). Recently, the Tp-Te interval has been identified as a reliable parameter to predict cardiac arrhythmias and sudden death (5). It has been shown that a prolonged Tp-Te interval and the Tp-Te/QT ratio, which are determined before revascularization during follow-up of patients experiencing ST-elevation myocardial infarction (STEMI), are associated with the incidence of cardiac events after discharge despite successful revascularization (6). Similarly, malignant arrhythmias such as ventricular tachycardia and fibrillation are more common in patients with a prolonged Tp-Te interval (7). In this study, we aimed to investigate if CAD severity could be estimated quickly and easily by measuring QT, cQT, Tp-Te, Tp-Te/QT in patients with NSTEMI.

METHODS

We retrospectively evaluated 277 patients who were hospitalized with the diagnosis of NSTEMI and underwent coronary angiography between October 2020 and February 2021. The diagnosis was based on the 2020 ESC NSTEMI-ACS guidelines (1). Patients with atrial fibrillation or atrial flutter or with an atrioventricular or intraventricular conduction defect; those with an implanted pacemaker, severe valvular disease, CAD, heart failure [ejection fraction (EF) <45%], renal failure, electrolyte disorders (hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypomagnesemia and hypermagnesemia) or hormone disorders (thyroid hormone disorder, adrenal hormone disorder); patients with a history of percutaneous intervention; or those receiving any anti-arrhythmic drug were excluded from the study. Thirty-six patients were excluded based on these criteria. Patients were treated according to the current guidelines. Patients were administered acetylsalicylic acid, clopidogrel, enoxaparin, beta-blockers, statins, and angiotensin-converting enzyme inhibitors unless they were contraindicated. This study was approved by the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Ethics Committee (decision no: 87, date: May 26, 2021).

Study Parameters

Patients' age, smoking status, comorbidities (diabetes mellitus, hypertension), family history of CAD, anthropometrics (body mass index, kg/m^2), hip circumference, and waist circumference were recorded. Patients were considered as having diabetes mellitus if they were using blood glucose-lowering drugs or had a fasting plasma blood glucose level ≥126 mg/dL or postprandial blood glucose ≥200 mg/dL. Hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or taking any antihypertensive medication.

Coronary Angiography and Syntax Score

Coronary angiography images were evaluated by two experienced interventional cardiologists who were blinded to the study data. CAD severity was determined using SS. Scoring was determined for each vessel that was >1.5 mm in diameter and had >50% stenosis. SS was calculated as described on the website in detail. Parameters including age, creatinine clearance, peripheral artery disease, chronic obstructive pulmonary disease, left ventricular EF, left common CAD, gender, SS, procedure-related complications, and the patient's prognosis were recorded (8). Patients were grouped based on the SS values, as follows: SS ≤22 and SS ≥22.

Electrocardiography

Each patient underwent a 12-lead ECG using the same device (Phillips page writer TC30, USA) at admission. ECG images with 10-s recordings at a speed of 25 mm/s and standard voltage of 1.0 mV (10 mm) were analysed. The interval between the beginning of the QRS wave and the termination of the T wave was measured using the QT tangent DII method. The measurements were made at the V5-V6 derivation when the T wave could not be evaluated. The corrected QT interval was calculated using Bazett's formula. The Tp-Te interval was measured at the V5 superficial derivation from the peak to the T wave termination. The measurements

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were made at the V4 or V6 derivation if it could not be read at the V5 derivation due to artefacts or low voltage (<0.15 mV). If the downslope of the T wave was inconclusive, the T wave was extended by drawing a tangent to the steepest portion of the downslope until it crossed the isoelectric line. All measurements were made by a single cardiologist (E.I.) who was blinded to the patient's data and using semi-automated on-screen software (EP Calipers v1.13, EP Studios, Inc., USA).

Reproducibility

Intraclass correlation coefficients were calculated for the intraindividual and interobserver variation. ECGs from 10 randomly assigned patients were re-analysed by the same observer. For interobserver variability, the same patients and the same images were analysed by a second observer (E.S.). In case of disagreement, the ECGs were referred to a third observer. The intra-observer correlation coefficients for Tp-Te and QT were 0.907 and 0.950, and the inter-observer correlation coefficients were 0.880 and 0.936, respectively.

Statistical Analysis

The data were presented as mean (standard deviation) or median (interquartile range) for continuous variables and as the percentage (n) for categorical variables. The normality of distribution for continuous variables was determined using the Kolmogorov-Smirnov test. The participants were divided into two distinct groups according to the SS. The normally and non-normally distributed continuous variables were compared using a Student's t-test and the Mann-Whitney U test, respectively. The frequency of categorical variables in these groups was compared using the Pearson chi-square test. The parameters distinguishing the groups at a significant level (age, presence of diabetes, QTc, Tp-Te interval, and Tp-Te/QT) were included in binary and multiple regression analyses. Finally, the predictive performance of the serum Tp-Te interval and Tp-Te/QT ratio was determined using the receiver operating characteristics (ROC) analysis. We performed the Spearman analysis to determine the correlation between the SS and repolarization markers. A p-value of <0.05 was considered to be significant in all studies. The confidence interval (CI) was accepted as 95%. Statistical Package for the Social Sciences (SPSS version 22.0, SPSS Inc., Chicago, IL, USA) was used for these assessments.

RESULTS

This study included 241 patients with a mean age of 62 (12) years. Patients were divided into groups based on the SS score as follows: low SS (SS <22; n=83) or high SS (SS ≥22; n=158). Baseline demographic and laboratory findings are shown in Table 1. No statistically significant difference was found between both groups in terms of gender (p=0.095), smoking (p=0.629), history of hypertension (p=0.625), dyslipidemia (p=0.755), and laboratory parameters (p>0.05). The high SS group was older, [57 (±10.43) vs. 70 (±8.87), p<0.001] and diabetes mellitus was more prevalent [75 (47%) vs. 54 (64%), p=0.014] compared to the low SS group.

In the ECG analysis, no statistically significant difference was observed in QT and corrected QT durations (p=0.272 and p=0.057, respectively) (Table 2). The Tp-Te interval [79.2 (±12.2) vs. 111.6 (±11.5), p<0.001], cTp-Te [87.7 (±14.5) vs. 116.6 (±15.8), p<0.001], and Tp-Te/QT [0.210 (0.029) vs. 0.243 (0.028), p<0.001] were statistically significantly higher in the high SS group compared to the low SS group (Figure 1).

Multivariate regression analysis was performed to determine the independent predictors. The Tp-Te interval [odds ratio (OR): 1.464, CI: 1.118-1.918; p=0.006] and Tp-Te/QT ratio (OR: 0.210, CI: 0.215-

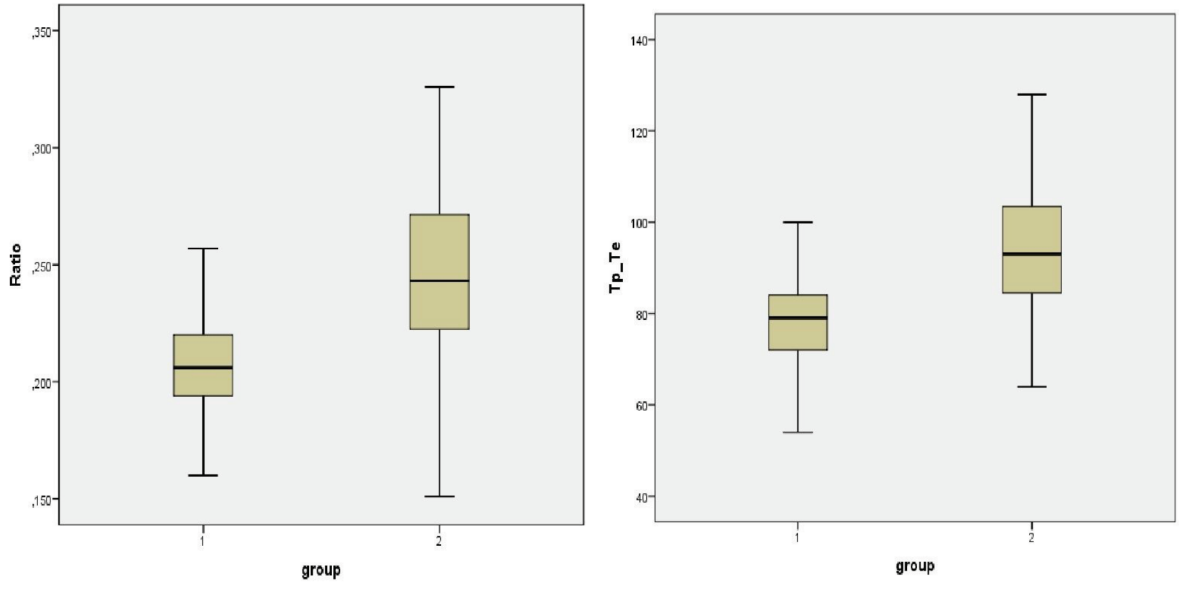

Figure 1. Comparison Tp-Te interval and Tp-Te/QT ratios between Syntax groups. Tp-Te interval and Tp-Te/QT ratio were significantly increased in the high Syntax score

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0.562; p<0.001) were found to be the independent predictors of a high SS score (Table 3). ROC analysis was performed to evaluate the predictive performance of Tp-Te and Tp-Te/QT levels to estimate a high SS. The ROC analyses showed that Tp-Te [area under the curve (AUC): 0.740, p<0.001] and Tp-Te/QT (AUC: 0.676, p<0.001) had a reasonable ability to predict severe CAD (Figure 2). The cut-off values for these parameters were 84.5 ms (with a sensitivity of 66.7% and specificity of 68.2%) and 0.219 (with a sensitivity of 72.01% and specificity of 65.2%), respectively. Spearman's analysis revealed that Tp-Te (rho =0.504, p<0.001) and Tp-Te/QT (rho =0.512, p<0.001) ratios were positively correlated with the SS (Figure 3).

DISCUSSION

In the present study, a strong correlation was found between the SS, which showed clinical and angiographic severity, and parameters that could be quickly studied using ECG results, such as the Tp-Te interval and Tp-Te/QT ratio.

The CAD severity is associated with the myocardial area that is at risk, increased plaque burden, degree of coronary stenosis, and multiple vessel disease. In addition, associated vasospasm affects perfusion disorder, and the ischemic area diffuseness (9).

Table 1. Demographic and laboratory features of the study population

	Overall (n=241)	Low Syntax score (n=158)	High Syntax score (n=83)	p-value
Age; mean ± (SD)	62 (12)	57 (10.43)	70 (8.87)	<0.001
Women, n (%)	132 (54.7%)	84 (53.1%)	48 (58%)	0.095
Diabetes mellitus, n (%)	125 (51%)	75 (47%)	54 (64%)	0.014
Hypertension, n (%)	106 (43.9%)	67 (42.4%)	33 (42%)	0.351
Smoker, n (%)	141 (58.5%)	63 (57.3%)	51 (60.7%)	0.629
LVEF, %; Median [IQR]	65 [45-65]	65 [44-65]	60 [40-65]	0.216
WBC, 10^3/dL; Median [IQR]	9.3 [6.8-10.1]	9.5 [7.1-9.7]	9.3 [6.7-9.6]	0.786
Platelet, 10^3/dL; Median [IQR]	233 [197-283]	230 [200-276]	234 [205-280]	0.901
C-reactive protein, mg/dL; Median [IQR]	8.3 [3.5-8.9]	8.4 [3.3-8.9]	8.1 [3.1-8.7]	0.560
Creatinine, mg/dL; Median [IQR]	0.96 [0.75-1.2]	0.95 [0.73-1.1]	0.90 [0.65-1.4]	0.719
Sodium, mEq/dL; Median [IQR]	139.3 [132-143]	139 [133-144]	139.2 [130-144]	0.725
Potassium, mEq/dL; Median [IQR]	4.28 [4.0-4.4]	4.30 [4.1-4.46]	4.25 [4.05-4.5]	0.439
HDL-C, mg/dL; Median [IQR]	41.5 [35-45]	41 [37-44]	41.5 [37.5-44.6]	0.934
LDL-C, mg/dL; Median [IQR]	107.5 [95-117]	110 [97-115]	106[93-113]	0.313
Triglyceride, mg/dL; Median [IQR]	186 [145-225]	188 [150-230]	195 [166-268]	0.503
Total cholesterol, mg/dL; Median [IQR]	190.5 [167-255]	200 [173-278]	189 [166-251]	0.755
RCA dominance, n (%)	162 (67)	102 (64)	60 (72)	0.236
Three-vessel disease, n (%)	29 (12)	12 (7)	17 (20)	<0.001
LMCA disease, n (%)	15 (6.2)	3 (1.9)	12 (14)	<0.001
Heavy calcification, n (%)	44 (18)	15 (9)	29 (35)	0.006
Thrombus, n (%)	71 (29)	40 (25.3)	31 (25.3)	0.086
Lesion length >20 mm, n (%)	141 (58)	91(58)	50 (60)	0.092
Chronic total occlusion, n (%)	77 (32)	44 (27.8)	33 (39.7)	0.095
Severe tortuosity, n (%)	20 (8)	11 (7.5)	9 (10.8)	0.573

HDL-C: high-density lipoprotein-cholesterol, IQR: interquartile range, LDL-C: low-density lipoprotein-cholesterol, LMCA: left main coronary artery, LVEF: left ventricular ejection fraction, RCA: right coronary artery, WBC: white blood cell, SD: standard deviation

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The SS was calculated by combining previous anatomical and physiological scores. The SS helped determine the degree and localization of the stenosis in CAD as well as the size of the myocardial area that is supplied by the affected artery and perfusion disorder (10-12).

Perfusion disorder causes differences in the oxygen level and chemical and electrical changes between cells. The degree of exposure to ischemia varies from cell to cell. Metabolic and electromechanical differences between normal or less affected cells and cells with necrosis include alterations in the membrane potential and dispersion in ventricular repolarization (11,13,14). This dispersion in the ventricular repolarization is shown on ECG as a prolongation of the Tp-Te interval.

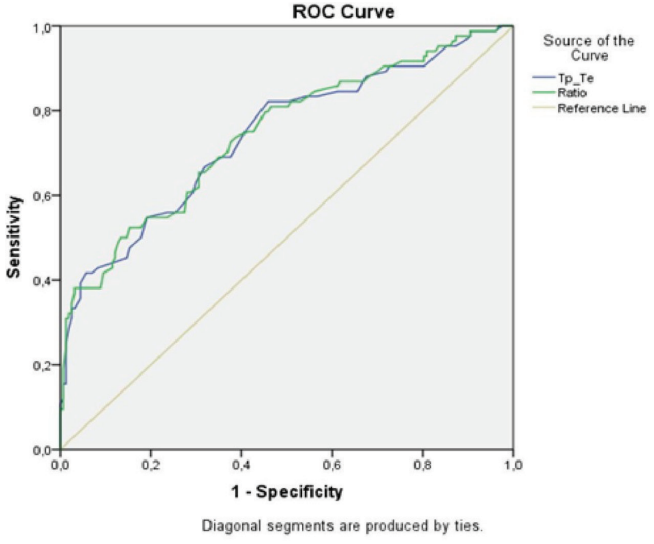

Figure 2. According to the ROC analyses, Tp-Te (AUC: 0.740, p<0.001), Tp-Te/QT (AUC: 0.676, p<0.001) had reasonable predictivity rates for severe coronary artery disease
ROC: receiver operating characteristics, AUC: area under the curve

Recent studies have revealed that changes in the Tp-Te interval and Tp-Te/QT ratio have a strong predictive value for estimating cardiac arrhythmias and cardiac events (15). Prolongation of the Tp-Te interval has been associated with sudden cardiac death and malignant arrhythmias in patients with ischemic and non-ischemic cardiomyopathies, congenital arrhythmia syndromes, and structural heart diseases (16). In a study in which patients were followed-up due to hypertrophic cardiomyopathy, the Tp-Te interval was reported to be a more specific marker than QT for predicting sudden cardiac death and ventricular fibrillation (17). In a study by Hetland et al. (18), a prolonged Tp-Te interval was found to be a predictor of ventricular arrhythmias, sudden cardiac death, and poor prognosis. Similarly, in a study by Özbek and Sökmen (19), an increased Tp-Te interval and Tp-Te/QT ratio measured before and after the intervention were associated with in-hospital and out-of-hospital mortality and the incidence of major cardiac events in patients with acute STEMI who were treated with percutaneous intervention or fibrinolytic therapy.

Besides ischemic conditions, Tp-Te and Tp-Te/QT parameters provide information about the disease severity and progression in patients with systemic inflammation (20). Current studies have proposed that the Tp-Te/QT ratio is a more accurate measurement for the distribution of ventricular repolarization compared to the QTd-cQTd duration (16-21). Although an elongation was found in the QT-cQT duration that showed general repolarization in cardiac ischemia, the parameters indicating dispersion in ventricular

Table 2. Electrocardiographic measurements of the study population

	Low Syntax score (n=158)	High Syntax score (n=83)	p-value
QT duration, ms; Median [IQR]	382 [356-410]	387 [360-408]	0.272
Corrected QT duration, ms; Median [IQR]	413 [396-425]	425 [415-445]	0.057
Tp-Te interval, ms; Mean (SD)	79.2 (12.2)	111.6 (11.5)	<0.001
Corrected Tp-Te interval, ms; Mean (SD)	87.7 (14.5)	116.6 (15.8)	<0.001
Tp-Te/QT ratio; Mean (SD)	0.210 (0.029)	0.287 (0.028)	<0.001

IQR: interquartile range, SD: standard deviation

Table 3. Multivariate predictors in high Syntax score

	Odds ratio	95% CI	p-value
Age	1.238	1.160-1.321	<0.001
Diabetes mellitus	0.610	0.277-1.343	0.219
Tp-Te interval	1.464	1.118-1.918	0.006
Corrected Tp-Te interval	0.978	0.907-1.054	0.557
Tp-Te/QT ratio	0.210	0.215-0.562	<0.001

CI: confidence interval

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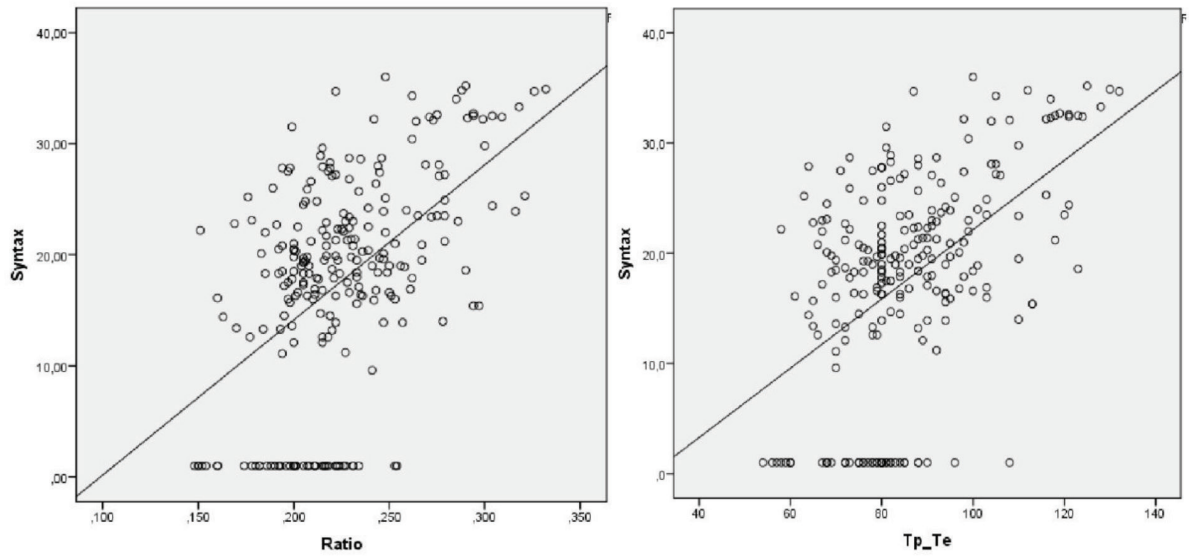

Figure 3. Correlation between the Syntax score and Tp-Te interval, Tp-Te/QT ratio. Tp-Te interval and Tp-Te/QT ratio were positively correlated with the Syntax scores

repolarization were more meaningful (22). Similarly, in our study, we found no significant difference in the QT-cQT duration.

In a recent study, the increase in the CAD spectrum from normal coronary arteries to acute coronary syndrome was found to be accompanied by a parallel prolongation in the Tp-e interval and increase in the Tp-e/QT and Tp-e/QTc ratios (23). Additionally, the same article stated that the CAD severity assessed using the SS was positively correlated with ventricular repolarization abnormalities in the Tp-e interval and the Tp-e/QT and Tp-e/QTc ratios, which was in agreement with our results. However, that article had only 121 patients with acute coronary syndrome (both STEMI and NSTEMI), and there was no grouping based on the SS. Our study adds value to the literature because it evaluates the relationship between ECG ventricular polarization parameters and CAD burden - assessed by the SS - in patients with NSTEMI.

Our hypothesis assumed that the increased CAD severity and diffuseness might lead to increases in ventricular repolarization duration and dispersion because it caused diffuse hypoxia and ischemia in the affected cardiac area and that this increase could be shown quickly and easily by measuring the following ECG parameters: QT, QTc, Tp-Te, and Tp-Te/QT. Results of our study showed that a high SS, which showed CAD severity and diffuseness were significantly correlated with Tp-Te and Tp-Te/QT, and the Tp-Te interval was an important predictor of a high SS.

Study Limitations

The retrospective and single-centre design of the study and the relatively small number of patients limited its strength. Previous studies focused on disease progression, and the patients were followed-up after revascularization. However, in the present study, the follow-up of the patients did not provide information about disease progression. Additionally, the semiautomatic nature of the ECG parameters rendered reaching standard values challenging. Although the sensitivity and specificity of the SS were high, intracoronary ultrasound, which offered information about coronary atherosclerosis, plaque burden, and thrombus burden, could not be used. Nevertheless, an extensive assessment of repolarization parameters may predict a more severe CAD burden in patients with NSTEMI.

CONCLUSION

This study indicates that calculating Tp-Te and Tp-Te/QT before an invasive procedure can provide information about CAD severity in hospitalized patients who are diagnosed as having NSTEMI. Prospective studies are needed to provide more information about the clinical outcomes in these risk-stratified patients according to the Tp-Te and Tp-Te/QT.

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Ethics Committee (no: KAEK/2021.05.87, date: May 26, 2021).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Author Contributions: Surgical and Medical Practices - B.A.; Concept - A.E.; Design - M.R.S.; Data Collection and/or Processing - B.A.; Analysis and/or Interpretation - Y.S.Ö.; Literature Search - E.Ö.; Writing - A.E.

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