



## The Relationship between Tpeak-end Interval Duration and Tpeak-end/QT Ratio, and Arrhythmias in Patients with Coronary Slow Flow

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### ABSTRACT

**Background:** Coronary Slow Flow (CSF) is described as delayed opacification of the distal vasculature and angiographically Normal Coronary Arteries (NCA). Numerous studies have suggested that the interval from the peak to the end of electrocardiographic T wave (Tp-e) may correspond to transmural dispersion of repolarization and that increased Tp-e interval and Tp-e/QT ratio are associated with malignant ventricular arrhythmias.

**Objectives:** The present study aimed to evaluate ventricular repolarization in patients with CSF by using Tp-e interval and Tp-e/QT ratio.

**Patients and Methods:** This study was conducted on electrocardiographic parameters of 100 patients with angiographically proven NCA with CSF in all three coronary arteries and 100 patients with NCA without CSF. The patients were followed up for arrhythmias and clinical events.

**Results:** Tp-e tail interval ( $120 \pm 5.5$  msn,  $101 \pm 3.9$  msn;  $P < 0.001$ ), Tp-e tangent interval ( $99 \pm 4.0$  msn,  $78 \pm 3.0$  msn,  $P < 0.001$ ), Tp-e tail/QT ratio ( $0.31 \pm 0.004$ ,  $0.26 \pm 0.003$ ,  $P < 0.001$ ), and Tp-e tangent/QT ratio ( $0.25 \pm 0.003$ ,  $0.19 \pm 0.003$ ,  $P < 0.001$ ) were significantly higher in the CSF patients compared to the NCA group. Rhythm holter analyses also showed that ventricular extrasystoles were higher ( $157 \pm 22.5$ ,  $87 \pm 11.9$ ,  $P = 0.002$ ) in the CSF group compared to the NCA group.

**Conclusions:** Tp-e interval and Tp-e/QT ratio were significantly higher in the patients with CSF compared to the NCA group.

#### ► Implication for health policy/practice/research/medical education:

Tp-e interval is an important electrocardiographic parameter to predict arrhythmias in patients with coronary slow flow.

### 1. Background

Coronary Slow Flow (CSF) is an angiographic finding characterized by delayed opacification of coronary arteries in the absence of epicardial occlusive disease. CSF is not a rare finding in patients undergoing routine coronary angiography and its prevalence has been reported to be 5.5% (1). Rather than representing a simple angiographic curiosity, CSF has direct clinical implications as it has been linked to clinical manifestations of myocardial ischemia,

life threatening arrhythmias, sudden cardiac death, and recurrent acute coronary syndromes (2-5).

T wave is the electrocardiographic manifestation of ventricular repolarization. Recent experimental evidences have suggested that the interval from the peak to the end of the T wave (Tp-e interval) corresponds to dispersion of ventricular repolarization (6-8). Increased Tp-e interval might be a useful index to predict ventricular tachyarrhythmias and cardiovascular mortality (9-11). Recently, a new index, Tp-e/QT ratio, has been suggested to be a more accurate measure for dispersion of ventricular repolarization compared to QT, corrected QT (QTc), and

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Tp-e intervals that are independent from alterations in heart rate (12, 13).

## 2. Objectives

The present study aims at evaluating the effects of CSF on Tp-e interval and Tp-e/QT ratio as a possible indicator of increased risk of ventricular arrhythmias and sudden cardiac death.

## 3. Patients and Methods

The study population included 100 patients with angiographically proven Normal Coronary Arteries (NCA) and CSF in all the three coronary vessels and 100 patients with angiographically proven NCA without associated CSF. Patients with left ventricular dysfunction, echocardiographically proven left ventricular hypertrophy, Electrocardiography (ECG) with atrial fibrillation, bundle branch block, and evidence of any other intraventricular conduction defects or electrolyte abnormalities were excluded from the study. In order to detect any possible arrhythmia, 24-hour rhythm holter monitoring was performed for all the patients within 48 hours after coronary angiography. The patients were followed by routine outpatient clinic visits. It should be mentioned that written informed consents were obtained from all the participants and the study protocol was approved by the local Ethics Committee.

### 3.1. Documentation of Coronary Slow Flow

After coronary angiography, the patients' coronary flow rates were documented by Thrombolysis in Myocardial Infarction (TIMI) frame count. The TIMI frame count method is a simple, reproducible, objective, and quantitative index of coronary flow velocity (14). The TIMI frame count was determined for each major coronary artery in each patient according to the method that was first described by Gibson et al. (14). Briefly, the number of cineangiographic frames, recorded at 30 frames per second, required for the leading edge of the column of radiographic contrast to reach a predetermined landmark was determined. The first frame was defined as the frame in which the concentrated dye occupied the full width of the proximal coronary artery lumen, touching both borders of the lumen, and in forward motion proceeded down the artery. Besides, the final frame was designated when the leading edge of the contrast column initially arrived at the distal landmark. In the Left Anterior Descending (LAD) coronary artery, the used landmark was the most distal branch nearest the apex of the left ventricle, commonly referred to as the "pitchfork" or the "whale's tail". LAD coronary artery is usually longer than the other major coronary arteries; therefore, the TIMI frame count is often higher for this vessel (15). To obtain a corrected TIMI frame count for LAD coronary artery, the TIMI frame count was divided by 1.7 (14).

The Right Coronary Artery (RCA) distal landmark is the first branch of the posteriolateral RCA after the origin of the posterior descending artery, regardless of the size of this branch. The branch of the Left Circumflex (LCx) artery that encompassed the greatest total distance traveled by contrast was used to define the distal landmark of the LCx

artery. The TIMI frame count was assessed in right anterior oblique projection with caudal angulation in the LAD and LCx arteries and in left anterior oblique projection with cranial angulation in the RCA.

### 3.2. Electrocardiography

All standard 12-lead ECGs were obtained at rest in the supine position simultaneously using a recorder (Nihon Kohden, Tokyo, Japan) set at 50 mm/s paper speed and 1 mV/cm standardization. Assessments of the ECGs were done by 2 cardiologists to diminish measurement errors. Lead V5 was selected for analysis. QRS interval duration and Tp-e interval duration measurements were made on lead V5. When the T wave in V5 was < 1 mm in height or was obscured by a large U wave, lead II was used. QT interval was measured in a single complex from the beginning of the QRS complex to the end of the T wave. QTc interval was the QT interval corrected with the Bazett's formula ( $QT/\sqrt{RR}$ ) (16). Besides, Tp-e was defined as the interval from the peak of a positive T wave or the nadir of a negative T wave to the end of the T wave in the tail method (17). In the tangent method, Tp-e (Tp-e tangent) was defined as the time from the peak of the T wave to the intersection between the tangent line and the isoelectric line (9, 18) (Figure 1). Although there is no consensus regarding heart rate correction of Tp-e, Bazett's formula ( $n/\sqrt{RR}$ ) was applied to Tp-e tail and Tp-e tangent intervals to determine cTp-e tail and cTp-e tangent, respectively. Tp-e/QT ratio was also calculated for all the ECGs. Although measurements were performed independently by two blinded physicians, when measurements were not identical, the mean values were calculated. Additionally, in case the values differed by > 10 ms, the measurements were adjudicated by a third reviewer.

### 3.3. Statistical Analysis

Continuous variables were expressed as mean  $\pm$  SEM, while categorical ones were expressed as percentage. The two groups were compared regarding categorical and continuous variables using chi-square test and unpaired t-test, respectively. In addition, the correlation between Tp-e and TIMI frame count was assessed by Pearson's correlation test. P value < 0.05 was considered to be statistically significant.

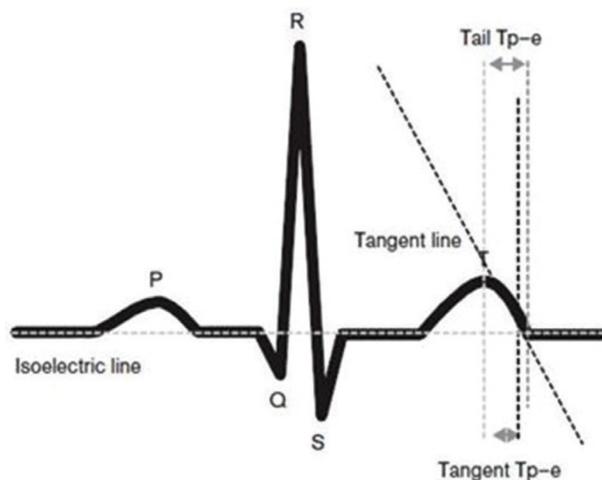


Figure 1. Schematic Presentation of Tp-e Measurement

#### 4. Results

The baseline characteristics of the study population have been presented in Table 1. Accordingly, no statistically significant differences were found between the two groups with respect to age, gender, and presence of hypertension and dyslipidemia ( $P > 0.05$ ). However, compared to the NCA group, the number of patients with diabetes mellitus, cigarette smoking, and family history of atherosclerosis was significantly higher in the CSF group. TIMI frame counts of the CSF group were also significantly higher than those of the NCA group for all the three coronary arteries ( $P < 0.001$  for all, Table 2).

Comparison of the ECG parameters has been presented in Table 3. Although the two groups were not different regarding QRS duration and QT and QTc intervals, Tp-e tail interval ( $120 \pm 5.5$  ms,  $101 \pm 3.9$  ms;  $P < 0.001$ ) and Tp-e tangent interval ( $99 \pm 4.0$  ms,  $78 \pm 3.0$  ms;  $P < 0.001$ ) were significantly prolonged in the CSF group compared to the NCA group. Also, Tp-e tail/QT ratio ( $0.31 \pm 0.004$ ,

$0.26 \pm 0.003$ ,  $P < 0.001$ ) and Tp-e tangent/QT ratio ( $0.25 \pm 0.003$ ,  $0.19 \pm 0.003$ ,  $P < 0.001$ ) were significantly higher in the CSF patients compared to the NCA group. In addition, a significant correlation was observed between Tp-e tail and TIMI frame counts ( $P < 0.001$ , Table 4).

The mean duration of coronary angiography follow-up was  $17 \pm 1.2$  months. The results of rhythm holter have been shown in Table 5. Accordingly, there were  $157 \pm 22.5$  and  $87 \pm 11.9$  Ventricular Extrasystoles (VES) in the CSF and NCA groups, respectively ( $P = 0.002$ ). Moreover, there were 6 case of non-sustained Ventricular Tachycardia (VT) in the CSF group (4 patients had 1 episode and 1 patient had 2 episodes) and 2 in the normal coronary flow group (2 patients had 1 episode) ( $P = 0.003$ ). Furthermore, a significant positive correlation was found between the number of VES and QTC interval ( $r = 0.195$ ,  $P = 0.024$ ).

#### 5. Discussion

The present study showed that Tp-e interval and Tp-e/QT

**Table 1.** Demographic Features of the Study Population

N = 200	CSF (n = 100)	NCA (n = 100)	P value
Age (year $\pm$ SEM)	$53.4 \pm 1$	$52.4 \pm 0.86$	0.431
Male/female	49/51	47/53	0.922
Hypertension (%)	62	48	0.073
Diabetes mellitus (%)	38	25	0.048
Dyslipidemia (%)	18	17	0.854
Family history (%)*	56	39	0.016
Smoking (%)	80	51	$< 0.001$
Systolic blood pressure (mmHg)	$128 \pm 1.95$	$128 \pm 1.7$	0.985
Diastolic blood pressure (mmHg)	$79.8 \pm 1.3$	$78.5 \pm 1.2$	0.626
Body mass index (kg/m <sup>2</sup> )	$28.4 \pm 0.37$	$27.8 \pm 0.29$	0.677
Ejection fraction (%)	$63 \pm 0.5$	$62 \pm 0.7$	0.888

\* Family history: First-degree relatives with coronary artery disease aging  $< 45$  years in men and  $< 55$  years in women.

**Table 2.** Thrombolysis in Myocardial Infarction Frame Counts of the Patients and the Control Subjects

N = 200	CSF (n = 100)	NCA (n = 100)	P value
LAD	$48.1 \pm 1.13$	$22.9 \pm 0.496$	$< 0.001$
LCx	$34.4 \pm 0.96$	$19.6 \pm 0.46$	$< 0.001$
RCA	$26.4 \pm 0.92$	$12.9 \pm 0.38$	$< 0.001$

Abbreviations: LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery

**Table 3.** Comparison of ECG Data Between the Patients

	CSF (n = 100)	NCA (n = 100)	P value
Heart rate (beats/min)	$74 \pm 0.6$	$72 \pm 0.5$	0.711
Tp-e tail (ms)	$120 \pm 5.5$	$101 \pm 3.9$	$< 0.001$
Tp-e tangent (ms)	$99 \pm 4.0$	$78 \pm 3.0$	$< 0.001$
QRS duration (ms)	$101.5 \pm 12.1$	$96.8 \pm 11.9$	0.122
QT interval (ms)	$392.1 \pm 14.9$	$390.3 \pm 4.32$	0.754
Corrected QT interval (ms)	$419.1 \pm 14.4$	$415 \pm 15.1$	0.524
Tp-e tail/QT	$0.31 \pm 0.004$	$0.26 \pm 0.003$	$< 0.001$
Tp-e tangent/QT	$0.25 \pm 0.003$	$0.19 \pm 0.003$	$< 0.001$

**Table 4.** The Correlation between Tp-e tail Duration and Thrombolysis in Myocardial Infarction Frame Count

N = 200	Pearson's Correlation	P value
LAD	0.62	$< 0.001$
CX	0.58	$< 0.001$
RCA	0.64	$< 0.001$

LAD, left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery

**Table 5.** The Results of the Patients' 24-hour ECG Holter Monitoring

N = 200	CSF (n = 100)	NCA (n = 100)	P value
Mean heart rate	85 ± 2.1	76 ± 1.9	0.44
Minimum heart rate	46 ± 0.5	48 ± 0.5	0.82
Maximum heart rate	145 ± 2.2	128 ± 2.0	0.25
Ventricular extra systole	157 ± 22.5	87 ± 11.9	0.003
Episodes of non-sustained VT*	6	2	0.002

\*Non-sustained VT: VT that lasts no longer than 30 seconds.

ratio were prolonged in the patients with CSF compared to those with normal coronary flow.

There has been considerable interest in the association between repolarization patterns and their electrocardiographic correlates and risk of arrhythmia. Tp-e interval may be a measure of transmural dispersion of recovery properties and many studies have shown that it is associated with arrhythmias. In addition, subsequent retrospective analyses in specific human populations, including those with acquired long QT syndrome, Brugada syndrome, and hypertrophic cardiomyopathy, showed Tp-e to be associated with torsades de pointes, appropriate Implantable Cardioverter Defibrillator (ICD) therapy, and sudden cardiac death, respectively (9, 18). Correspondingly, holter analysis of our patients showed that number of VES and non-sustained VT were significantly higher in the patients with CSF compared to those with NCA. The patients with CSF also had more cardiovascular risk factors, such as diabetes, smoking, and positive family history. These factors might have also caused VES via development of atherosclerosis. However, all the patients underwent angiography and they did not have obstructive Coronary Artery Disease (CAD). In a small case-control study on a heterogeneous population of patients undergoing Electrophysiology Study (EPS), Watanabe et al. showed that inducibility of VT at EPS correlated to longer corrected Tp-e duration (13). In patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction, a longer pre-PCI (but not post-PCI) Tp-e predicted all-cause one-year mortality (12). In patients with left ventricular systolic dysfunction and ICD therapy, Tp-e predicted both appropriate ICD therapy for ventricular tachyarrhythmia and overall mortality, even after correction for other independent predictors (14).

Slow runoff dye in the coronary arteries during selective coronary angiography is known as slow coronary artery flow (19). Since its original description by Tambe et al. in 1972, only scarce attention has been paid to this phenomenon and, consequently, its clinical significance has remained unclear. Some authors suggested that abnormal increase of small vessel resistance was the cause of the slow dye progression in selective coronary angiography (20-22). It is believed to represent coronary microvascular dysfunction. Histopathological studies have also revealed the existence of fibromuscular hyperplasia, medial hypertrophy, myointimal proliferation, and endothelial degeneration in microvascular circulation from the right ventricular biopsy specimens of patients with slow coronary artery flow (21). It has been suggested that these histopathological changes lead to an abnormally increased microvascular tone and, as a result, most patients with CSF complain mainly about typical angina

pectoris. Yaymaci et al. documented the presence of myocardial ischemia in 83.4% of these patients with positive scintigraphic findings (23). Furthermore, some researchers have shown exercise-induced ST-segment depression in patients with CSF without obstructive CAD (23, 24). Therefore, increased Tp-e durations in patients with CSF might be attributed to impaired coronary blood flow, which might result from microvascular dysfunction. Coronary insufficiency caused by impaired coronary blood flow seems to be the most valuable explanation for increased left ventricular repolarization heterogeneity in patients with CSF.

In conclusion, the current study results revealed that Tp-e and Tp-e/QT, indicating increased risk of ventricular arrhythmias and cardiovascular mortality, were significantly higher in the patients with CSF. However, further prospective studies should be carried out to establish the significance of Tp-e and Tp-e/QT, as risk factors of ventricular arrhythmias and the subsequent sudden cardiac death, in patients with CSF.

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#### Authors' Contribution

Study concept and design: Fatih Sen, Samet Yilmaz; Acquisition of data: Fatih Sen; Analysis and interpretation of data: Samet Yilmaz; Drafting of the manuscript: Firat Ozcan; Critical revision of the manuscript for important intellectual content: Ozcan Ozeke; Statistical analysis: Dursun Aras, Administrative, technical, and material support: Serkan Topaloglu; Study supervision: Sinan Aydođdu

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