

ORIGINAL ARTICLE

Effects of the Coronary Collateral Circulation on the Tp-e Interval and Tp-e/QT Ratio in Patients with Stable Coronary Artery Disease

Hakan Taşolar, M.D.,* Mehmet Ballı, M.D.,* Mustafa Çetin, M.D.,*
Yılmaz Ömür Otlı, M.D.,† Burak Altun, M.D.,‡ and Adil Bayramoğlu, M.D.§

From the *Adiyaman University Training and Research Hospital, Department of Cardiology, Adiyaman, Turkey; †Kars State Hospital, Department of Cardiology, Kars, Turkey; ‡18 Mart University Faculty of Medicine, Department of Cardiology, Çanakkale, Turkey; and §Elbistan State Hospital, Department of Cardiology, Kahramanmaraş, Turkey

Background: The clinical utility of the Tp-e interval and Tp-e/QT ratio in the risk stratification of ventricular arrhythmic events is controversial. Therefore, we investigated the impact of CCC on these electrocardiographic indexes in the course of stable CAD.

Methods: Two hundred three consecutive patients with stable CAD who underwent coronary angiography and had documented total occlusion of one of the major coronary arteries were enrolled in this prospective cross-sectional study. The Tp-e interval and Tp-e/QT ratio were measured by 12-lead electrocardiogram.

Results: The Tp-e interval, cTp-e interval, Tp-e/QT ratio, and cTp-e/QT ratio were lower in the grade 3 CCC group compared with the others in all leads. Multivariate linear regression analyses was performed to identify the clinical factors affecting the cTp-e interval and was indicated that age ($\beta = 0.261$, $P < 0.001$), male sex ($\beta = 0.334$, $P < 0.001$), poor Rentrop grade ($\beta = -0.228$, $P < 0.001$), and NLR ($\beta = 0.137$, $P = 0.027$) were independent predictors of a prolonged cTp-e interval.

Conclusion: It could be concluded that the decreased dispersion of ventricular repolarization might contribute to the lower incidence of ventricular arrhythmias and SCD in CAD patients with a good CCC.

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coronary artery disease; coronary collateral circulation; Tp-e interval; ventricular arrhythmogenesis

The coronary collateral circulation (CCC) constitutes an alternative blood source for ischemic myocardium in coronary artery disease (CAD). A well-developed CCC can limit ischemic damage, reduce infarct size, and improve survival.¹ Moreover, a well-developed CCC is associated with a lower incidence of malignant arrhythmias and with reduced risks of all-cause mortality and sudden cardiac death (SCD) in patients with stable CAD.^{2,3}

Increased dispersion of repolarization, which reflects the heterogeneity rather than the total

duration of repolarization, is a known pathogenic factor in malignant ventricular arrhythmias.⁴ The Tp-e interval is a novel index of the transmural dispersion of ventricular repolarization and is related to SCD risk.⁵ Myocardial repolarization can also be evaluated using the QT interval (QT) or QT dispersion (QTd). The Tp-e/QT and cTp-e/QT ratios can also be used as electrocardiographic indices of ventricular arrhythmogenesis.⁶

Neutrophil-lymphocyte ratio (NLR) determines systemic inflammatory response and has been

Address for correspondence: Dr. Hakan Taşolar T.C. Sağlık Bakanlığı Adiyaman Üniversitesi Eğitim ve Araştırma Hastanesi Hastane Cad. Merkez/Adiyaman, Turkey. Fax: +9 0 416 214 25 25; E-mail: hakantasolar@gmail.com

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proposed as a prognostic marker in CAD patients.⁷ The NLR shows the balance of the neutrophils (the active component of the inflammation), with the lymphocytes (the regulatory and protective component).⁷ Previous studies have indicated that higher levels of NLR are linked with adverse outcomes and increased cardiovascular mortality in patients with CAD.^{8,9}

There are few studies about the clinical utility of the Tp-e interval and Tp-e/QT ratio in the risk stratification of ventricular arrhythmic events. Therefore, we investigated the impact of CCC on these ventricular arrhythmia indexes in the course of stable CAD.

METHODS

Study Population

Between April 2008 and October 2013, 203 consecutive patients (134 men; mean age 63.6 ± 10.9 years) with stable CAD who underwent coronary angiography in our hospital and had documented total occlusion of one of the major coronary arteries were enrolled in this prospective cross-sectional study.

Patients who had a myocardial infarction within the previous month, history of revascularization (coronary artery bypass graft operation or percutaneous coronary intervention), active angina, severe valvular or congenital heart disease, hepatic or renal dysfunction, asthma or reactive bronchospastic airway disease, thyroid disturbances, pericardial effusion, serum electrolyte imbalance, documented paroxysmal atrial fibrillation, an electronic cardiac pacemaker, sick sinus syndrome, bundle branch block, preexcitation syndromes, atrioventricular block, or technically inadequate coronary angiography were excluded from the study. Patients diagnosed with hematological disease, cancer, acute/chronic infective or inflammatory disease, or autoimmune disease were also excluded. All patients were in sinus rhythm at referral, and none were taking any medicine that could affect the Tp-e interval.

The ejection fraction, presence of hypertension and diabetes mellitus, and their influences on the results were investigated. HT was diagnosed if the systolic blood pressure was ≥ 140 mm Hg or the diastolic blood pressure ≥ 90 mm Hg in at least two separate readings, or if the patient was

taking any antihypertensive medication. DM was defined as a fasting blood glucose level ≥ 126 mg/dL on two separate occasions or if the patient was being treated with oral antihyperglycemic agents or insulin. Smoking status was defined as currently smoking. The local ethics committee approved the study protocol, and informed written consent was obtained from each patient.

Coronary Angiography and Assessment of the CCC

Coronary angiography was done through the femoral artery using the Judkins technique for all patients. Two specialists who were blinded to the clinical details and results of the other investigations interpreted the coronary arteriographic data of each patient to assess the coronary artery lesion and CCC. If there was disagreement between the two cardiologists, the angiograms were evaluated by a third cardiologist and a consensus was reached. To classify the CCC, we used the Rentrop classification.¹⁰ The grades of collateral filling from the contralateral vessels were as follows: 0 = no filling of any collateral vessel; 1 = filling of side branches of the artery to be perfused by the collateral vessels without visualization of the epicardial segment; 2 = partial filling of the epicardial segment by collateral channels; and 3 = complete filling of the epicardial segment of the artery being dilated through collateral channels.¹⁰ When more than one occluded vessel was present, the one with the highest Rentrop grade was recorded. The study population was then classified according to their CCC grades into poor (Rentrop grades 0 or 1) and good (Rentrop grades 2 or 3) groups. The intra- and interobserver variability of the Rentrop classification was assessed using 40 subjects selected randomly from the study participants (20 patients each with poor and good CCC). The intraobserver variability was 2.8% and the interobserver variability 3.1%.

Biochemical and Hematological Parameters

Blood samples were taken after a 12-hour fast on the day of admission. Kidney function, lipid profiles, and fasting glucose levels were analyzed for all patients (Architect c 16000, Abbott Diagnostics, Lake Forest, IL, USA). Hematological

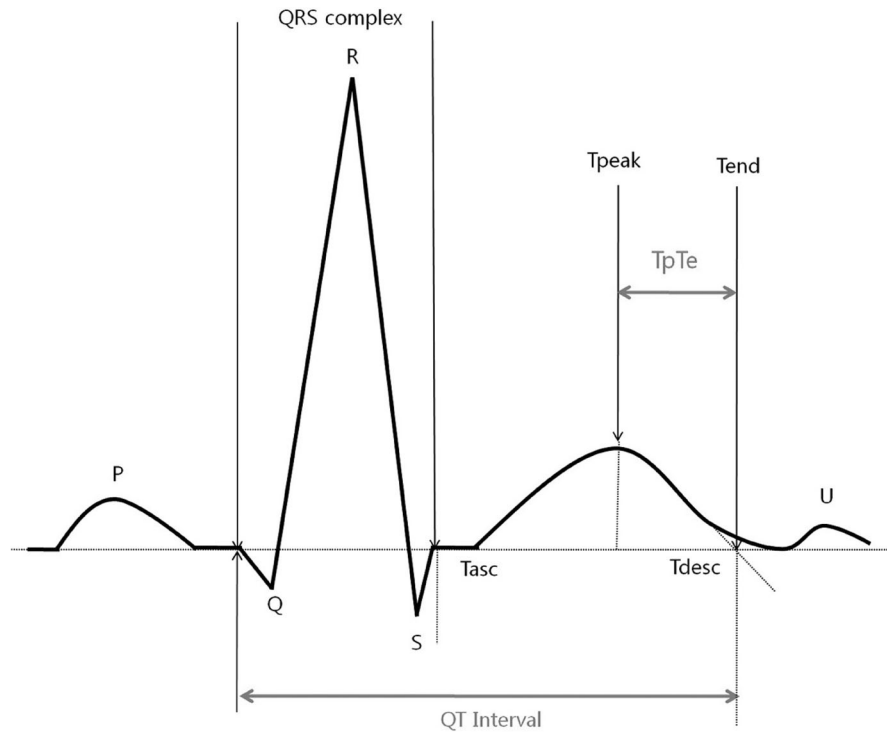


Figure 1. This figure is highlighting the electrocardiographic parameters measured when assessing the QT interval and the interval from the peak to the end of the T wave (Tp-e interval).⁹

parameters were measured using an automatic blood counter (Cell Dyn 3700 Abbott Diagnostics).

Measuring the Tp-e and QT Intervals from the 12-Lead ECG

A 12-lead electrocardiogram (ECG) was obtained at a paper speed of 50 mm/s with an amplification of 20 mm/mV. The heart rate was measured from the ECG data. Two cardiologists measured the Tp-e and QT intervals manually from the ECG using calipers and a magnifying glass to decrease measurement errors. The average value of three measurements was calculated for each lead. The QT interval was measured from the beginning of the QRS complex to the end of the T wave and was corrected for heart rate using Bazett's formula ($QT_c = QT/\sqrt{RR}$).¹¹ The QTd was defined as the difference between the maximum and minimum QT intervals, and the QTc dispersion was defined as the difference between the maximum and minimum QTc intervals.¹¹

The Tp-e interval was defined as the interval from the peak of a T wave to the end of that

T wave. The end of the T wave was described as the intersection of the tangent of the descending limb of the T wave with the isoelectric line (Fig. 1).¹² The Tp-e interval was measured from leads II, V₂, and V₅ and corrected for the heart rate (cTp-e).¹³ When a U wave followed the T wave, the T-wave offset was measured as the nadir between the T and U waves. If T-wave deflections resulted in a biphasic or negative T wave, the QT interval was measured from the time of the final return to baseline. If the T-wave amplitude was less than 1.5 mm in a lead, that lead was excluded from the analysis. The Tp-e/QT and cTp-e/QT ratios were calculated from these values. The intra- and interobserver variability of the cTp-e interval was assessed using 40 randomly selected study participants (20 patients each with poor and good CCC). The intraobserver variability was 2.5%, and the interobserver variability was 2.6%.

Statistical Analysis

The statistical analysis was performed using SPSS for Windows 17.0 (Chicago, IL, USA). Data

Table 1. Clinical Characteristics, Laboratory, and Echocardiographic Findings of the Study Population

	Poor CCC (n = 75)	Good CCC (n = 128)	P value
Baseline characteristics			
Age (years)	63.1 ± 10.7	63.8 ± 11.1	0.638
Men, n (%)	55 (73.3)	79 (61.7)	0.093
Body mass index (kg/m ²)	22.1 ± 1.98	21.8 ± 1.5	0.909
Hypertension, n (%)	38 (50.7)	62 (48.4)	0.761
Diabetes, n (%)	26 (34.7)	48 (37.5)	0.658
Smoking, n (%)	32 (42.7)	63 (49.2)	0.369
Ejection fraction, %	51.8 ± 7.4	51.1 ± 7.9	0.488
Laboratory findings			
Glucose (mg/dL)	101.5 ± 17.8	101.8 ± 21.4	0.904
Creatinine (mg/dL)	1.0 ± 0.2	0.9 ± 0.3	0.690
HDL(mg/dL)	39.4 ± 11.4	38.1 ± 10.3	0.490
LDL(mg/dL)	78.2 ± 21.2	73.8 ± 23.4	0.189
Triglyceride (mg/dL)	99.6 ± 22.9	95.9 ± 25.9	0.312
Hemoglobin (mg/dL)	12.9 ± 2.1	13.0 ± 2.0	0.841
Neutrophile, × 10 ⁹ /L	6.79 ± 2.98	4.96 ± 1.99	<0.001
Lymphocyte, × 10 ⁹ /L	2.08 ± 0.70	2.32 ± 0.78	0.032
Neutrophile/lymphocyte ratio	3.65 ± 1.99	2.42 ± 1.44	<0.001
Medication, n (%)			
Acetylsalicylic acid	59 (78.7)	93 (72.7)	0.343
Beta-blockers	37 (49.3)	68 (53.1)	0.604
ACE inhibitors/ARBs	27 (36.0)	46 (35.9)	0.993
Calcium channel blockers	13 (17.3)	23 (18.0)	0.909
Statins	53 (70.7)	86 (67.2)	0.606
Occluded artery, n (%)			
LAD	33 (44.0)	53 (41.4)	0.390
CX	18 (24.0)	38 (29.7)	0.384
RCA	34 (45.3)	74 (57.8)	0.088

CCC = coronary collateral circulation; HDL = high-density lipoprotein; LDL = low-density lipoprotein; ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; LAD = left anterior descending; CX = circumflex; RCA = right coronary artery.

were tested for normal distribution using the Kolmogorov-Smirnov test. Differences between the groups were evaluated using the independent-samples *t*-test and one-way analysis of variance, with post hoc Tukey's test, where appropriate. Categorical variables were compared using the chi-square test. Continuous variables were expressed as the mean ± standard deviation and categorical data as numbers and percentages. Pearson and Spearman correlation tests were used to evaluate the associations between the Tp-e interval and the study parameters. Linear multiple stepwise regression analysis was used to evaluate the association between a prolonged cTp-e interval and independent variables that differed significantly in the univariate analyses ($P < 0.1$). A P value < 0.05 was considered statistically significant.

RESULTS

The study population consisted of 203 patients with stable CAD (75 with poor CCC, 128 with good CCC). Table 1 compares the clinical, laboratory, and angiographic characteristics of the patients according to collateral development. Both groups were similar in terms of age, gender, body mass index, left ventricular ejection fraction, and medication usage. In addition, there were no significant differences in the presence of hypertension, diabetes mellitus, smoking, or hypercholesterolemia between the groups. When compared to the patients with good CCC, the patients with poorly developed CCC had significantly higher neutrophil and lymphocyte counts and NLR.

Table 2. Electrocardiographic Findings of the Study Population

		Grade 0 (n = 44)	Grade 1 (n = 31)	Grade 2 (n = 40)	Grade 3 (n = 88)	P value
Heart rate (beat/min)		58.7 ± 14.5	60.5 ± 6.3	59.9 ± 5.3	60.1 ± 5.8	0.809
QT interval (ms)	II	366.7 ± 20.7	365.9 ± 20.4	363.9 ± 27.0	369.8 ± 19.3	0.495
	V ₂	375.2 ± 18.8	374.3 ± 14.2	377.7 ± 24.3	376.4 ± 15.3	0.863
	V ₅	358.5 ± 19.4	357.4 ± 13.7	361.3 ± 19.9	364.3 ± 14.0	0.118
QT dispersion of the 12 leads (ms)		35.0 ± 9.3	36.1 ± 9.3	34.6 ± 8.9	34.7 ± 7.3	0.869
QTc interval (ms)	II	372.4 ± 30.7	366.5 ± 23.4	362.7 ± 24.9	369.4 ± 26.4	0.348
	V ₂	381.2 ± 31.8	375.1 ± 22.6	376.6 ± 23.9	375.8 ± 20.2	0.635
	V ₅	364.0 ± 29.7	358.1 ± 21.2	360.4 ± 19.6	363.9 ± 20.1	0.563
QTc dispersion of the 12 leads (ms)		38.6 ± 9.5	39.1 ± 9.9	37.9 ± 9.5	37.9 ± 7.8	0.910
cTp-e interval (ms)	II	74.5 ± 5.7	72.6 ± 8.4	74.5 ± 7.6	67.8 ± 5.8	<0.001 ^a
	V ₂	78.7 ± 5.5	76.4 ± 8.3	79.2 ± 7.1	71.8 ± 5.8	<0.001 ^a
	V ₅	70.4 ± 5.4	68.4 ± 9.2	70.1 ± 7.7	62.9 ± 5.8	<0.001 ^a
cTp-e interval (ms)	II	75.6 ± 7.0	72.7 ± 8.7	74.4 ± 8.3	67.7 ± 5.8	<0.001 ^a
	V ₂	79.9 ± 6.9	76.5 ± 8.8	79.1 ± 8.1	71.7 ± 5.9	<0.001 ^a
	V ₅	71.5 ± 6.6	68.4 ± 9.3	70.0 ± 8.6	62.9 ± 6.0	<0.001 ^a
Tp-e/QT ratio	II	0.19 ± 0.02	0.20 ± 0.02	0.21 ± 0.02	0.18 ± 0.02	<0.001 ^a
	V ₂	0.21 ± 0.03	0.21 ± 0.02	0.21 ± 0.02	0.19 ± 0.02	0.001 ^a
	V ₅	0.19 ± 0.02	0.19 ± 0.02	0.19 ± 0.02	0.18 ± 0.02	<0.001 ^a
cTp-e/QT ratio	II	0.20 ± 0.01	0.20 ± 0.02	0.21 ± 0.02	0.18 ± 0.01	<0.001 ^a
	V ₂	0.21 ± 0.02	0.20 ± 0.02	0.21 ± 0.02	0.19 ± 0.02	<0.001 ^a
	V ₅	0.20 ± 0.20	0.019 ± 0.03	0.20 ± 0.02	0.17 ± 0.02	<0.001 ^a

QTc = corrected QT; cTp-e = corrected Tp-e.

^aDifferences were found between the Grade 3 compared with the other groups, other binary comparisons were nonsignificant.

Table 2 presents the ECG findings according to the Rentrop grade. The heart rate, QT interval, QTd, QTc interval, and QTc dispersion were similar among the groups. The Tp-e interval (Fig. 2), cTp-e interval, Tp-e/QT ratio, and cTp-e/QT ratio were lower in the grade 3 CCC group compared with the others in all leads.

The correlations between the cTp-e interval in lead V₅ and the study parameters are presented in Table 3. There were significant correlations between the cTp-e interval and age ($P < 0.001$), male sex ($P < 0.001$), neutrophil count ($P = 0.038$), NLR ($P < 0.001$), and poor Rentrop grade ($P < 0.001$).

Table 4 shows the results of the multivariate linear regression analyses performed to identify the clinical factors affecting the cTp-e interval. These indicated that age ($\beta = 0.261$, $P < 0.001$), male sex ($\beta = 0.334$, $P < 0.001$), poor Rentrop grade ($\beta = -0.228$, $P < 0.001$), and NLR ($\beta = 0.137$, $P = 0.027$) were independent predictors of a prolonged cTp-e interval.

DISCUSSION

This study evaluated the effects of the CCC on the Tp-e interval and Tp-e/QT ratio as indices of ventricular arrhythmogenesis in patients with CAD. Our results showed that: (i) the patients with good CCC had significantly lower neutrophil and lymphocyte counts and a NLR than the patients with a poorly developed CCC; (ii) the Tp-e and cTp-e intervals and Tp-e/QT and cTp-e/QT ratios were lower in the patients with grade 3 CCC; and (iii) age, male sex, NLR, and poor Rentrop grade were independent predictors of a prolonged cTp-e interval in patients with CAD.

Although CAD is the condition mostly associated with SCD,¹⁴ no studies have clearly shown the effects of CCC on ventricular arrhythmias in CAD patients. Increased CCC is reported to reduce the vulnerability of the myocardium to ventricular fibrillation.¹⁵ Nagomoto et al. found that stopping the CCC flow to an occluded artery led to an increased frequency of ventricular tachycardia and ventricular premature beats in the ischemic

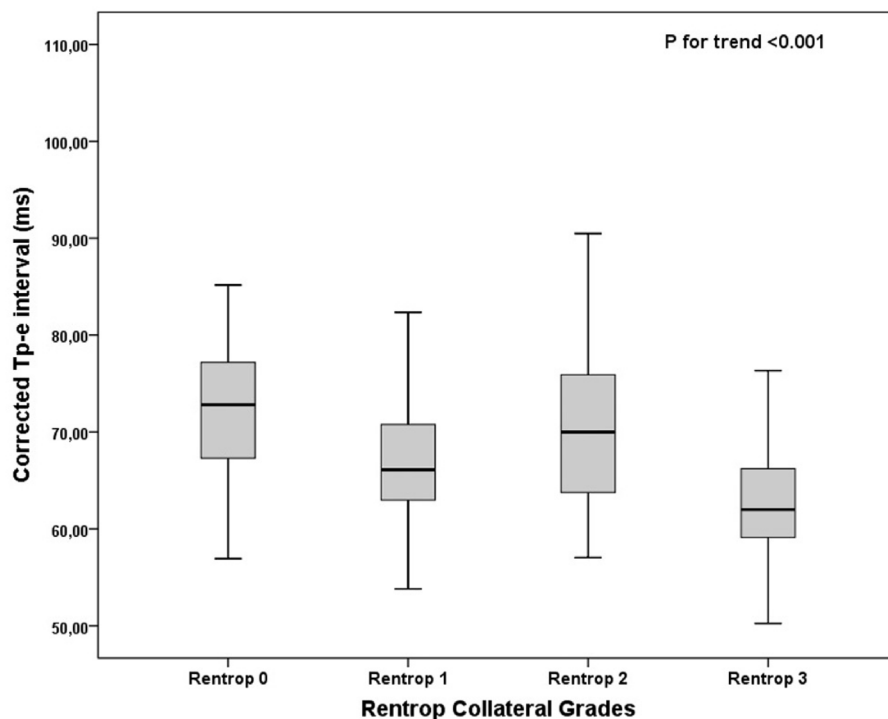


Figure 2. Relationship between corrected Tp-e interval and Rentrop score (error bars: 95% confidence interval [CI]).

tissue.¹⁶ Given the limited information, we assessed the relationship between the QT and Tp-e intervals, as indices of ventricular arrhythmias, and the grade of CCC in patients with CAD who had at least one occluded coronary artery.

Although the development of CCC is a chronic adaptation to myocardial ischemia, its exact mechanism is not known. Sufficient CCC reduces ischemic damage and infarct size and improves survival in CAD patients.^{3,17-19} Nonfatal cardiovascular events are also less common in patients with a CCC in the setting of stable CAD.^{20,21} The grade of CCC varies markedly among patients, and the heterogeneity of the degree of CCC in CAD patients is uncertain. In addition to growth factors, inflammatory cell mediators, endothelial chemokines, oxidative stress, smoking, endothelial dysfunction, DM, HT, and the severity and progression of coronary stenosis can affect the development of coronary collateralization.^{22,23} Inflammation also plays a significant role in all stages of atherosclerosis, as well as in the development of CCC.²⁴ Uysal et al. found that the NLR was significantly higher in patients with a poor CCC and concluded that a high NLR was

associated with the development of CCC in stable CAD patients. In line with this, our patients with good CCC had a lower NLR. Although NLR was an independent predictor of a prolonged cTp-e interval in our series, it is not clear whether this is a result of CCC formation, in which the NLR is involved, or a direct effect of the NLR. This needs to be clarified with further studies.

Amplification of the dispersion of ventricular repolarization is a predictor of ventricular arrhythmias.⁶ An increased QTd reflects inhomogeneous ventricular repolarization that might predispose to important ventricular arrhythmias. Changes in QTd associated with an acute myocardial infarction (MI) suggest that transient ischemic episodes in patients with stable CAD are important. Since most of the SCD in this population likely originates from ischemia-related arrhythmias, it is obvious that the CCC has an important role in patients with CAD who have at least one totally occluded artery. Nevertheless, studies evaluating the QT dispersion in CAD patients have revealed contradictory results. Yılmaz et al.²⁵ found that the rest-corrected QTd was increased in CAD patients. Meier et al.²⁶ also stated that myocardial ischemia

Table 3. Correlation of Study Parameters with cTp-e Interval

Parameters	cTp-e interval	
	R	P value
Age	0.286	<0.001
Male sex	0.447	<0.001
Body mass index	-0.063	0.375
Hypertension	-0.111	0.116
Diabetes	-0.009	0.897
Ejection fraction	-0.059	0.402
Smoking	-0.024	0.739
Glucose	-0.112	0.111
Creatinine	-0.104	0.141
HDL	-0.054	0.447
LDL	0.055	0.435
Triglyceride	0.077	0.272
Neutrophile	0.146	0.038
Lymphocyte	-0.053	0.457
Neutrophile/lymphocyte ratio	0.213	<0.001
Acetylsalicylic acid	0.051	0.468
Beta-blockers	-0.072	0.310
ACE inhibitors/ARBs	-0.071	0.313
Calcium channel blockers	-0.040	0.566
Statins	0.037	0.601
LAD	0.079	0.264
CX	-0.004	0.952
RCA	-0.082	0.246
Rentrop grade	-0.455	<0.001

HDL = high-density lipoprotein; LDL = low-density lipoprotein; ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; LAD = left anterior descending; CX = circumflex; RCA = right coronary artery.

leads to QT prolongation, which is inversely related to collateral function, indicating a protective mechanism of human coronary collaterals against cardiac death. Countering these studies, Tandogan et al. could not identify positive or corrective effects of the CCC on the corrected QTd, and they even noted higher corrected QTd values when a well-developed CCC was present.²⁷ In accordance with the latter study, we found that the presence of a CCC had no effect on the QTd.

Several studies have shown that the Tp-e interval, as a sensitive index of arrhythmogenesis, corresponds to the dispersion of ventricular repolarization.^{4,28,29} Therefore, it has attracted increased attention in the last few decades.⁶ Panikkath et al. found that prolongation of the Tp-e interval was independently associated with SCD in CAD patients, and this was particularly beneficial when the QTc interval was normal.³⁰ Wang et al. found that Tp-e prolongation was associated

Table 4. Multivariate Analysis to Demonstrate Independent Predictors of Prolonged cTp-e Interval

Independent variables	β	P value ^a
Age	0.261	<0.001
Male sex	0.334	<0.001
Rentrop grade	-0.228	<0.001
Neutrophile/lymphocyte ratio	0.137	0.027

^aLinear regression analyses using the stepwise method were used for the multivariate analysis of independent variables that were included if they were significantly different in the univariate analyses (P < 0.1).

with more cardiac events in Brugada syndrome.³¹ Recently, Erikssen et al. reported that the Tp-e interval, particularly the cTp-e interval, was a strong predictor of mortality in acute MI patients.³² Although studies have reported the utility of the Tp-e interval as an arrhythmogenic index in some cardiac conditions associated with an increased risk of malignant arrhythmia and SCD,^{33,34} no study has evaluated the effect of the CCC on this ECG parameter in CAD patients.

Women with known CAD are at a lower risk of SCD than men.³⁵ Korantzopoulos et al. found that women with CAD have a lower Tp-e interval and a lower Tp-e/QT ratio than men and postulated that the increased dispersion of ventricular repolarization contributes to the higher risk of ventricular arrhythmias and SCD in men with CAD.³⁶ In line with these data, we evaluated the effect of the CCC on the Tp-e interval in CAD patients and found that the CAD patients with a good CCC had shorter Tp-e intervals than patients with a poor CCC. Furthermore, this decline was negatively correlated with the Rentrop grade. We also found that age, male sex, NLR, and Rentrop grade were independent predictors of a prolonged cTp-e interval in patients with CAD. These results seem to support our hypothesis; nevertheless, since our study was a cross-sectional design, prospective studies with longer follow-up are needed to clarify the precise effects of the CCC on ventricular arrhythmias and SCD using the cTp-e interval.

Study Limitation

The cross-sectional design of the study limited the follow-up in terms of ventricular arrhythmias and SCD and was a main limitation of our study.

Another limitation was the difficulty determining the nature of the CCC, which might have affected our results. Collaterals become visible angiographically only after they reach a diameter of 100 μ m, and collaterals with smaller diameters cannot be observed angiographically. We can determine only a minor part of the collateral network, and it is impossible to observe intramural collaterals angiographically.³⁷

CONCLUSION

We found that the cTp-e interval and cTp-e/QT ratio were lower in the patients with grade 3 CCC and that age, male sex, the NLR, and Rentrop grade were independent predictors of a prolonged cTp-e interval in patients with CAD. Therefore, the decreased dispersion of ventricular repolarization might contribute to the lower incidence of ventricular arrhythmias and SCD in CAD patients with a good CCC.

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