ORIGINAL ARTICLE

New Markers for Ventricular Repolarization in Coronary Slow Flow: Tp-e Interval, Tp-e/QT Ratio, and Tp-e/QTc Ratio

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Background: Coronary slow flow (CSF) is characterized by normal or near-normal coronary arteries with delayed opacification of the distal vasculature that it may cause angina pectoris, acute myocardial infarction, life-threatening arrhythmias, and sudden cardiac death. The Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio are also known as predictors of ventricular arrhythmogenesis. The aim of this study was to assess ventricular repolarization in patients with CSF by using Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio.

Methods: This study included 50 patients with CSF and 51 control subjects. Coronary flow rates of all subjects were documented by thrombolysis in myocardial infarction (TIMI) frame count (TFC). Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were measured from the 12-lead electrocardiogram. These parameters were compared between groups.

Results: In electrocardiographic parameters analysis, QT, QTc, QTd, and QTcd were significantly increased in CSF patients compared with the control subjects ($P < 0.001$, $P = 0.019$, $P < 0.001$, $P < 0.001$, respectively). The Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio in the CSF patients were significantly higher than those in the control subjects (Tp-e: 117 ± 21 milliseconds [ms] vs 96 ± 16 ms, $P < 0.001$; Tp-e/QT: 0.30 ± 0.06 vs 0.27 ± 0.06, $P = 0.005$; Tp-e/QTc: 0.27 ± 0.06 vs 0.24 ± 0.05, $P < 0.001$). In the multivariate analysis, increased Tp-e and Tp-e/QT ratio were associated with CSF.

Conclusions: Our study revealed that when compared to the control subjects, Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc were significantly increased in the CSF patients.

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coronary slow flow; ventricular repolarization; Tp-e interval; Tp-e/QT ratio; Tp-e/QTc ratio

Coronary slow flow (CSF) is frequently seen in patients undergoing routine coronary angiography and is characterized by delayed opacification of normal coronary arteries in the absence of epicardial occlusive disease.[1,2] The incidence of CSF is reportedly 1% among patients undergoing coronary angiography,[3] and it is seen in 1–5.5% of patients undergoing coronary angiography for suspicion of acute coronary syndrome.[4] CSF was indicated in 10–30% of patients evaluated for typical angina, who had normal coronary arteries on angiography.[1,5] Several mechanisms have been proposed for CSF, including decreased nitricoxide levels, microvascular abnormalities, diffuse

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atherosclerosis, and endothelial dysfunction.[6,7] However, the etiopathogenesis of CSF is complicated and not yet fully understood.

The T wave is an electrocardiographic parameter indicative of myocardial repolarization. Myocardial repolarization can be assessed based on the QT interval (QT), corrected QT interval (QTc), QT dispersion (QTd), and dispersion of ventricular repolarization; these values are associated with an increased risk of cardiac arrhythmias.[8] Nonspecific repolarization changes and arrhythmias are seen on electrocardiography (ECG) in patients with CSF.[9,10] Sudden cardiac death due to CSF is thought to occur because of arrhythmias originating from myocardial ischemia.[10,11] Tp-e, which is the interval between the peak and the end of the T wave on ECG, is accepted as an index of dispersion of ventricular repolarization.[11,12] The Tp-e interval, Tp-e/QT, and Tp-e/QTc ratios are used as a new electrocardiographic index of ventricular arrhythmogenesis.[13]

In this study, we assessed the myocardial repolarization in patients with CSF using the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio.

METHODS

Study Design

The present study was cross-sectional and observational.

Study Population

The study population included 50 patients with angiographically proven normal coronary arteries and CSF in at least one coronary vessel (22 females; mean age 52 ± 10 years), and 51 patients with angiographically proven normal coronary arteries without CSF (27 females; mean age 52 ± 9 years) were included in this study. All patients had chest pain or angina equivalent symptoms with either positive treadmill test or myocardial perfusion study. Ethics committee approval and informed consent was obtained from all patients. Exclusion criteria were patients with moderate to severe valvular heart disease, coronary artery disease, coronary plaque, prosthetic heart valve, bundle branch block, atrial fibrillation, paced rhythm, coronary artery ectasia, previous history of myocardial infarction, uncontrolled hypertension, hypertrophic or dilated cardiomyopathies, congenital heart disease, hyperthyroidism, hypothyroidism, malignancy, pulmonary, hepatic or renal dysfunction.

Diagnosis of CSF and Thrombolysis in Myocardial Infarction (TIMI) Frame Count (TFC)

Coronary angiography was performed for all patients using the Siemens Artis zee flor (Erlangen, Germany) with the standard Judkins technique in multiple angulated views. During the procedure, iohexol 350/100 mL was used as a contrast agent and manually injected (5–6 mL contrast agent at each position) in all patients. Angiographies were recorded at a speed of 30 frames/second.

The diagnosis of CSF was made using the TFC method, first described by Gibson et al.[14] In this method, the number of cineangiographic frames, recording 30 frames per second, required for the leading edge of the column of radiographic contrast to first reach standard distal coronary landmarks in the left anterior descending (LAD), circumflex (Cx), and right coronary arteries (RCA) was recorded using the cine viewer frame counter. Distal landmark was defined as distal bifurcation for the LAD and the Cx and first branch of posterolateral artery for RCA. The measurement of TFC for each artery was done by subtracting the first frame from the last frame. Since LAD coronary artery is usually longer than the Cx and RCA, the TFC for the LAD is often higher. Therefore, the LAD frame counts were corrected by dividing by 1.7 to derive the corrected TFC as described earlier.[14] The standard mean values for normal visualization of coronary arteries are described as 36.2 ± 2.6 frames for the LAD, 22.2 ± 4.1 frames for the Cx, and 20.4 ± 3 frames for the RCA. The corrected cutoff value for the LAD was 21.1 ± 1.5 frames as previously described.[14] TFC in the LAD and Cx were assessed in the right anterior oblique projection with caudal angulation and RCA in left anterior oblique projection with cranial angulation. For objective quantification of the coronary flow, two independent observers, blinded to the clinical data of the study subjects, assessed the coronary flow in coronary arteries using TFC method. Any values in excess of these thresholds were considered as CSF.

Electrocardiography

Twelve-lead ECGs were obtained at rest, with 10 mm/mV amplitude and 25 mm/sec (Cardiofax V; Nihon Kohden Corp., Tokyo, Japan) rate with the patient in the supine position and breathing freely. ECGs were obtained within one hour before coronary angiography. All of the ECGs were transferred to a PC via a scanner and then used for ×400% magnification by Adobe Photoshop software, which measurements were made on the computer by two cardiologists who were blinded to the status of each patient and control subject. Patients were excluded if these points were not clear.

RR interval, QRS duration, QT and QTd were measured in all derivations. QT was defined as the time from the start of the QRS to the point at which T wave returns to isoelectric line, and average value of two readings was calculated for each lead. The QTc was calculated by using the Bazett's Formula:[15] $QTc = QT/\sqrt{R - R}$ interval. QTd was defined as the difference between the longest and shortest QT interval of the 12 leads. The QTc dispersion (QTcd) was defined as the difference between the maximum and the minimum QTc interval of the 12 leads. Subjects with U waves on their ECGs were excluded from the study. RR interval measured as the average of three complexes.

The Tp-e interval was measured via tail method. In this method, the Tp-e interval was defined as the time from the peak or nadir of the T wave to the point where the wave reached the isoelectric line.[13] Measurements of Tp-e interval were performed from precordial derivations, lead V_2 was selected for measuring. The Tp-e/QT and Tp-e/QTc ratios were calculated from lead V_2. To improve the reliability of T wave off set determination, leads with low-amplitude T waves (<0.1 mV) were excluded from analysis. Intraobserver and interobserver variabilities in Tp-e were 4.2% and 6.7%, respectively.

Echocardiography

In all subjects, two-dimensional transthoracic echocardiography was performed using 2.5–3.5 MHz transducer (General Electric Vivid S5, Milwaukee, WI, USA) in the left decubitus position. Left ventricular (LV) diameter and thickness were measured with two-dimensional targeted M-mode echocardiography; however, LV ejection fraction (LVEF) was assessed by the biplane modified Simpson method, using the criteria of the American Society of Echocardiography.[16] LV end-systolic and end-diastolic volumes (LVESV and LVEDV) were calculated using the biplane modified Simpson's rule in the apical 4- and 2-chamber views at end systole and diastole. LV volume indexes were then calculated as LV volumes divided by body surface area.

Statistical Analysis

Statistical analyses were performed using SPSS software (version 15.0, SPSS, Chicago, IL, USA). According to Kolmogorov–Smirnov normality test, two independent-sample *t*-tests were used to compare the normally distributed independent variables between two groups, and Mann–Whitney U test was used to compare the non-normally distributed independent variables between two groups. Normally distributed continuous data were expressed as mean ± standard deviation; non-normally distributed continuous variables were presented as median and interquartile range (Quartiles 1–3). Chi-square test was used for comparing the categorical data. Categorical data were expressed as count and percentages. Multivariate logistic regression was used to identify the independent predictors of CSF. P-value <0.05 was considered significant.

RESULTS

The baseline characteristics, echocardiographic, and angiographic findings of the patients with CSF and control subjects are listed in Table 1. Distributions of age, sex, smoking, hyperlipidemia, hypertension, diabetes mellitus, body mass index (BMI), body surface area (BSA), systolic and diastolic blood pressure, LV diameters, LV volumes and volume indexes, and LV ejection fraction were similar between the two groups. However, TFC values were significantly higher in the CSF group compared with the control group (Table 1).

The electrocardiographic parameters of the groups are shown in Table 2. QT, QTc, QTd, and QTcd were significantly increased in CSF patients compared with the control subjects ($P < 0.001$, $P = 0.019$, $P < 0.001$, $P < 0.001$, respectively). The Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio in the CSF patients were significantly higher

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

Variables	CSF (–) (n = 51)	CSF(+) (n = 50)	P
Age, years	52.8 ± 9.12	52.9 ± 10.3	0.944
Sex, female	27 (52.9)	22 (44.0)	0.369
Smoking	13 (25.5)	11 (22.0)	0.680
Hyperlipidemia	17 (33.3)	19 (38.0)	0.624
Hypertension	15 (29.4)	21 (42)	0.187
Diabetes mellitus	6 (11.8)	10 (20)	0.257
BMI, kg/m^2	29 ± 4.82	30.1 ± 4.88	0.240
BSA, m^2	1.78 ± 0.14	1.78 ± 0.16	0.989
Systolic BP, mmHg	127 ± 22	128 ± 19	0.790
Diastolic BP, mmHg	75 [70–86]	80 [70–85]	0.391
LVEDD, mm	49.0 ± 4.1	49.6 ± 5.1	0.525
LVESD, mm	29.5 ± 6.8	31.6 ± 4.6	0.073
LVEDV, mL	121.3 ± 13.9	120.4 ± 14.9	0.736
LVESV, mL	44.8 ± 5.6	44.6 ± 5.9	0.863
LVEDV index, mL/m^2	68.3 ± 9.6	68 ± 11.1	0.883
LVESV index, mL/m^2	25.2 ± 3.6	25.2 ± 4.5	0.969
LVEF, %	63.7 ± 2.5	63.1 ± 2.7	0.760
TFC LAD	35 [34–37]	50 [42–68]	**<0.001**
TFC Cx	22 [21–23]	29 [22–36]	**<0.001**
TFC RCA	22 [20–23]	30 [26–37]	**<0.001**

BMI = body mass index; BP = blood pressure; BSA = body surface area; CSF = coronary slow flow; Cx = circumflex artery; LAD = left anterior descending artery; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; RCA = right coronary artery; TFC = TIMI (thrombolysis in myocardial infarction) frame count.
Data are presented as mean ± SD, median [interquartile range], or n (%). Statistically significant P values shown in bold.

Table 2. Electrocardiographic Findings of the Study Groups

Variables	CSF (–) (n = 51)	CSF(+) (n = 50)	P
HR, beat/min	76 ± 11	73 ± 12	0.187
QT, ms	366 ± 34	392 ± 38	**<0.001**
QTd, ms	30 ± 19	44 ± 19	**<0.001**
QTc, ms	409 ± 37	425 ± 33	**0.019**
QTcd, ms	34 [19–42]	49 [33–66]	**<0.001**
Tp-e, ms	96 ± 16	117 ± 21	**<0.001**
Tp-e/QT	0.27 ± 0.06	0.30 ± 0.06	**0.005**
Tp-e/QTc	0.24 ± 0.05	0.27 ± 0.06	**<0.001**

CSF = coronary slow flow; HR = heart rate; QTc = corrected QT; QTcd = corrected QT dispersion; QTd = QT dispersion; Tp-e = T wave peak-to-end interval.
Data are presented as mean ± SD or median [interquartile range]. Statistically significant P values shown in bold.

than those in the control subjects (Tp-e: 117 ± 21 milliseconds [ms] vs 96 ± 16 ms, P < 0.001; Tp-e/QT: 0.30 ± 0.06 vs 0.27 ± 0.06, P = 0.005; Tp-e/QTc: 0.27 ± 0.06 vs 0.24 ± 0.05, P < 0.001). Multivariate logistic regression model adjusted with age, sexual status (male), smoking, and LV volume indexes was constituted to identify for the predictors of CSF in the study group (Table 3). In the multivariate analysis, Tp-e (odds ratio [OR] 1.21, 95% confidence interval [CI]: 1.11–1.32; P < 0.0001) and Tp-e/QT ratio (OR 1.13, 95% CI: 1.04–1.19; P = 0.009) were found to be independent predictors of CSF.

DISCUSSION

In the present study, in electrocardiographic recordings from patients with CSF documented by the TFC, Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio were significantly greater than those of control subjects. In the multivariate analysis, Tp-e and Tp-e/QT ratio were independent predictors of CSF (P < 0.05).

CSF is characterized by normal or near-normal coronary arteries with delayed opacification of the distal vasculature. It was first described by Tambe et al.[1] The incidence of CSF is reportedly 1% among patients undergoing coronary angiography.[3] This phenomenon may cause angina pectoris, acute myocardial infarction, life-threatening arrhythmias, and sudden cardiac death.[11,17,18] The exact pathophysiological mechanisms of CSF are unclear. The

Table 3. Multivariate Logistic Regression Analyses of Independent Variables for Coronary Slow Flow

Variables	OR	% 95 CI for OR		P
		Lower	Upper	
Tpe, ms	1.21	1.11	1.32	**<0.0001**
QTd, ms	1.02	0.99	1.05	0.259
Tpe/QT	1.13	1.04	1.19	**0.009**
Age, years	0.98	0.92	1.04	0.458
Sex, male	2.65	0.76	9.24	0.126
Smoking	0.84	0.21	3.45	0.813
LVEDV index, mL/m^2	1.02	0.91	1.15	0.719
LVESV index, mL/m^2	0.89	0.66	1.22	0.477

LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; QTd= QT dispersion; Tp-e = T wave peak-to-end interval; CI = confidence interval; OR = odds ratio. Statistically significant P values shown in bold.

main reasons for CSF are thought be microcirculation disorders, endothelial dysfunction, decreased nitricoxide levels, increased vasoconstrictor responses, and inflammation.[19–21] There are multiple histopathological features associated with CSF.[17,22] Mosseri et al.[22] found fibromuscular hyperplasia, medial hypertrophy, myointimal proliferation, and endothelial degeneration of the microvascular circulation in right ventricular biopsy specimens from patients with CSF.

Recent studies demonstrated myocardial ischemia in 28–75% of patients with CSF having positive scintigraphic findings.[23,24] In addition, Pekdemir et al.[25] demonstrated a decreased fractional flow reserve in patients with CSF, and they reported that these patients had increased resistance due to diffuse atherosclerosis in the epicardial coronary arteries by intravascular ultrasonography. Myocardial ischemia at the microvascular level may explain the increased Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio. The relationship between CSF and increased QTd, myocardial infarction, ventricular fibrillation, and sudden cardiac death due to myocardial ischemia has also been shown in previous case reports and clinical studies.[11,18,26] Myocardial ischemia due to increased resistance in the epicardial coronary arteries and intramyocardial fibrosis derived from the examination of biopsy specimens[25] may be the underlying mechanisms of arrhythmias in patients with CSF. The authors stated that these abnormalities could be due to pathophysiological factors. Although the exact mechanisms of arrhythmia in CSF are unknown, recent studies reported that dispersion of ventricular repolarization might play an important role in the formation of ventricular arrhythmias.

The QT and QTc intervals are indicative of ventricular repolarization on ECG. Prolonged QT and QTc intervals have been reported in a number of cardiovascular diseases linked to an increased risk of ventricular tachycardia/fibrillation, torsades de pointes, and sudden cardiac death.[27–29] Sezgin et al.[30] reported a similar QT interval but significantly longer QTc interval in CSF patients, as compared to control subjects. Atak et al.[26] showed that the QTc intervals of CSF patients were similar to those of control subjects. In this study, we found that the QT and QTc intervals were significantly increased in CSF patients compared with control subjects.

The QTd and QTcd indicate the dispersion of ventricular repolarization. Increased QTd and QTcd durations are generally associated with the dispersion of ventricular repolarization and are accepted as markers for arrhythmia and sudden death.[29,31] Previous studies showed that the QTcd was significantly higher in patients with CSF.[26,30,32] Likewise, in our study, we found significant differences in QTcd between CSF patients and control subjects. Data on the effects of CSF on QTd duration are limited. Several investigators have studied ventricular repolarization patterns in patients with CSF, and they showed that the QTd value was increased, as compared to control subjects.[30,33] We found that the QTd value was significantly increased in CSF patients, as compared to control subjects.

The T wave is an electrocardiographic finding indicative of ventricular repolarization. The Tp-e interval, which is the interval between the peak and the end of a single T wave on ECG, can be used as an index of the total dispersion of ventricular repolarization. An increased Tp-e interval is associated

with malignant ventricular arrhythmias and cardiovascular events.[8,29,34] However, the Tp-e interval is affected by variations in body weight and heart rate.[13] Recently, new indexes, the Tp-e/QT and Tp-e/QTc ratios, were suggested to be a more accurate measure of the dispersion of ventricular repolarization, as compared to the QTd, QTcd, and Tp-e intervals, and to be independent of alterations in heart rate.[13,35] Hence, the Tp-e/QT and Tp-e/QTc ratios have emerged as novel electrocardiographic markers of an increased dispersion of ventricular repolarization.[13,36] Our study is the first to evaluate the Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio in patients with CSF.

Several studies have shown that the Tp-e interval may provide an index of the dispersion of ventricular repolarization and that it may be used to predict life-threatening arrhythmias in patients with Brugada syndrome, long QT syndrome, and in patients undergoing primary percutaneous coronary intervention for myocardial infarction.[8,37,38] Panikkath et al.[39] reported that prolongation of the Tp-e interval was associated with sudden cardiac death. Similar to these studies, we found that the Tp-e interval was significantly prolonged in patients with CSF.

There are limited data on the Tp-e/QT and Tp-e/QTc ratios in patients with CSF. The Tp-e/QT and Tp-e/QTc ratios are new parameters for predicting the risk of arrhythmia in different diseases. Obstructive sleep apnea (OSA) is related to an increased risk of ventricular arrhythmias and sudden cardiac death.[40,41] Kilicarslan et al.[36] reported that the Tp-e/QT and Tp-e/QTc ratios were increased in OSA. Furthermore, it was reported that the Tp-e/QT ratio was increased in systemic lupus erythematosus[42] and rheumatoid arthritis.[43] In our study, we found significant differences in the Tp-e/QT and Tp-e/QTc ratios between CSF patients and control subjects.

We propose that an increased Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio may result from coronary ischemia secondary to CSF, and that an increased Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio may have a prognostic role in detecting myocardial ischemia.

Study Limitations

Our study has some limitations. Small number of the patients included in the study is the major limitation. Owing to a limited number of patients may have negatively affected the statistical power of the study. Additionally, the present study was performed at a single center. Our findings must be confirmed via prospective, multicenter studies. In addition, patients could not be followed prospectively for ventricular arrhythmic episodes. Therefore, larger and longer-term follow-up should strengthen the value of the results. Finally, the prognostic role of Tp-e interval, Tp-e/QT, and Tpe/QTc ratios in patients with CSF needs to be investigated.

CONCLUSIONS

CSF is associated with a prolonged Tp-e interval and increased Tp-e/QT and Tp-e/QTc ratios. Based on these findings, ECG can be used to help determine the risk of life-threatening arrhythmias in patients with CSF. Further study is required to evaluate the prognostic significance of the dispersion of ventricular repolarization to clarify the mechanism of increased Tp-e, Tp-e/QT, and Tp-e/QTc values in CSF.

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