Eurasian J Med 2015; 47: 104-8 The Eurasian Journal of Medicine **Original Article**

Evaluation of Tp-Te Interval and Tp-Te/QT Ratio in Patients with Coronary Slow Flow Tp-Te/QT Ratio and Coronary Slow Flow

Koroner Yavaş Akımlı Hastalarda Tp-Te Aralığının ve Tp-Te/QT Oranının Değerlendirilmesi

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Abstract

Objective: Coronary slow flow (CSF) phenomenon is described by angiographically normal coronary arteries with delayed opacification of the distal vasculature. Several studies have suggested that the interval from the peak to the end of the electrocardiographic T wave (Tp-Te) may correspond to the transmural dispersion of the repolarization and that increased Tp-Te interval and Tp-Te/QT ratio are associated with malignant ventricular arrhythmias. The aim of this study was to evaluate the ventricular repolarization by using Tp-Te interval and Tp-Te/QT ratio in patients with CSF.

Materials and Methods: This study included 50 CSF patients (40 male, mean age 48.6±12.5 years) and 40 control individuals (23 male, mean age 47.8±12.5 years). Tp-Te interval and Tp-Te/QT ratio were measured from the 12-lead electrocardiogram. These parameters were compared in groups.

Results: Baseline characteristics of the study groups were comparable. In electrocardiographic parameters analysis, QT and corrected QT were similar in CSF patients compared to the controls (357±35.2 vs 362±38.0 milliseconds and 419±25.8 vs 430±44.2 milliseconds, all p value >0.05). Tp-Te interval, Tp-Te/QT and Tp-Te/QTc ratio were significantly higher in CSF patients (85±13.7 vs 74±9.9 milliseconds and 0.24±0.03 vs 0.20±0.02 and 0.20±0.03 vs 0.17±0.02 all p value <0.001).

Conclusion: Our study revealed that QTd, Tp-Te interval and Tp-Te/QT ratio are prolonged in patients with CSF.

Keywords: Coronary slow flow, arrhythmia, Tp-Te interval, Tp-Te/QT ratio

Özet

Amaç: Koroner yavaş akım (KYA) uzak damarların opaklaşmasında gecikme ile birlikte anjiyografik olarak normal koroner arterleri tanımlayan bir fenomendir. Çeşitli çalışmalar elektrokardiyografik T dalgasının tepe noktasından sonuna kadar olan intervalin (Tp-Te) repolarizasyonun transmural dağılımına uygun olabileceğini ve artmış Tp-Te intervali ve Tp-Te/QT oranının malign ventriküler aritmiler ile ilişkili olduğunu ileri sürmüşlerdir. Bu çalışmanın amacı, KYA olan hastalarda Tp-Te intervali ve Tp-Te/QT oranı kullanılarak ventriküler repolarizasyonu değerlendirmekti.

Gereç ve Yöntem: Bu çalışma 50 KYA hastasını (40 erkek, ortalama yaş 48,6±12,5 yıl) ve 40 kontrol bireyi (23 erkek, ortalama yaş 47,8±12,5 yıl) kapsamaktaydı. Tp-Te intervali ve Tp-Te/QT oranı 12-kanallı elektrokardiyogram ile ölçüldü. Bu parametreler gruplar arasında karşılaştırıldı.

Bulgular: Çalışma gruplarının başlangıç özellikleri kıyaslanabilirdi. Elektrokardiyografik parametrelerin analizde, QT ve düzeltilmiş QT kontrollere kıyasla KYA hastalarında benzerdi (362±38,0'e karşılık 357±35,2 milisaniye ve 430±44,2'ye karşılık 419±25,8 milisaniye, tümü için p değeri >0,05). Tp-Te intervali, Tp-Te/QT ve Tp-Te/QTc oranı KYA hastalarında anlamlı olarak yüksekti (74±9,9'a karşılık 85±13,7 milisaniye ve 0,20±0,02'ye karşılık 0,24±0,03 ve 0,17±0,02'ye karşılık 0,20±0,03, tümü için p değeri <0,001).

Sonuç: Çalışmamız KYA olan hastalarda QTd, Tp-Te intervali ve Tp-Te/QT oranının uzamış olduğunu ortaya koydu.

Anahtar Kelimeler: Koroner yavaş akım, aritmi, Tp-Te intervali, Tp-Te/QT oranı

Introduction

Coronary slow flow (CSF) is characterized by delayed opacification of the coronary arteries in the absence of obstructive coronary artery disease (CAD) in coronary angiography [1].

Several mechanisms have been proposed for the aetiology of CSF, including microvascular and endothelial dysfunction, small vessel disease, diffuse atherosclerosis and inflammation. However, its etiopathogenesis is still not clear [2, 3]. Coronary atherosclerosis, disturbed microvascularizа-

This study was presented at the Frontiers in Cardiovasculer Biology as e-poster, 4-6 July, Barcelona, Spain.

Received: July 24, 2014 / **Accepted:** October 02, 2014

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DOI:10.5152/eurasianjmed.2015.72

tion functions, and endothelial dysfunction were reported to be closely related to CSF [4, 5]. It was shown that there is significant relationship between inflammatory markers and coronary flow rate [6, 7].

This phenomenon has been associated with the increased risk of ventricular arrhythmias and sudden cardiac death. Impaired myocardial blood flow in CSF may cause fatal cardiac arrhythmias by bringing about electrical abnormalities during ventricular repolarization [8].

Myocardial repolarization has been evaluated by various methods including QT dispersion (QTd), corrected QT dispersion (cQTd), and transmural dispersion of repolarization. Recent studies indicated that T wave peak to T wave end (Tp-Te) interval, which is the interval between the peak and the end of T wave on electrocardiogram (ECG), can be used as an index of total (transmural, apico-basal, and global) dispersion of repolarization [9-11]. Also, increased Tp-Te interval might be a useful index to predict ventricular tachyarrhythmia and cardiovascular mortality [12-15]. Recently, a new index, the Tp-Te/QT ratio has been suggested to be a more accurate measure for the dispersion of ventricular repolarization compared to QTd, cQTd, and Tp-Te intervals which are independent of alterations in heart rate [16, 17]. The novel repolarization indexes Tp-Te interval and Tp-Te/QT ratio, is not studied in these patients before.

The aim of this study was to evaluate the repolarization dispersion measured from the 12- lead surface electrocardiogram (including Tp-Te interval and Tp-Te/QT ratio) in patients with CSF.

Materials and Methods

Patients

The study group included 50 patients (40 male, mean age 48.6±12.5 years) with isolated CSF without any stenotic lesions under visual assessment. The control group consisted of 40 age- and gender-matched subjects (23 male, mean age 47.8±12.5 years) who proved to have normal coronary angiograms. The study was approved by the Institutional Ethics Committee, and written consent was obtained from all patients.

The indication for the coronary angiography was either the presence of typical angina or positive or equivocal results of non-invasive screening tests for myocardial ischemia in both groups.

Physical examination, medical history of patients, blood biochemistry and transthoracic echocardiographic examination were evaluated in both groups to exclude systemic diseases. Patients with obstructive coronary artery disease (who had coronary stenotic lesions of >20%), chronic renal failure, any stage of hypertension, left ventricle hypertrophy, chronic liver disorders, chronic lung disease, moderate or severe valvular disease, atrial fibrillation, bundle branch block or evidence of any other intraventricular conduction defect, prior pacemaker implantation, congenital heart disease, left ventricular systolic dysfunction on echocardiography (EF<50%), obstructive sleep apnoea, thyroid dysfunction are excluded from the study.

Coronary Angiography

Coronary angiograms were performed with a femoral approach using the Judkins technique without the use of nitro-glycerine, adenosine, or a calcium channel blocker. All patients in the study population underwent elective coronary artery angiography using Siemens Axiom Artis DFC (Siemens Medical Solutions, Erlangen, Germany) following appropriate patient preparation. Coronary angiograms were judged with regard to smooth appearance, luminal wall irregularities, epicardial local or diffuse calibre reduction, and stenosis.

Coronary arteries were demonstrated at least four views of the left coronary system using 6 French left coronary catheters and two views of the right coronary artery using 6 French right coronary catheters by 15 fps rate in the same cardiac catheterisation laboratory. Coronary blood flow was measured quantitatively using the thrombolysis in myocardial infarction frame count (TFC). Initial frame count is defined as the frame in which concentrated dye occupies the full width of proximal coronary artery lumen, touching both borders of the lumen, and forward motion down the artery. The final frame is designated when the leading edge of the contrast column initially arrives at the distal end. Distal end was defined as distal bifurcation for the left anterior descending (LAD) artery, the distal bifurcation of the segment with the longest total distance for the circumflex artery (CX), and the first branch of the posterolateral artery for the right coronary artery (RCA). LAD coronary artery is usually longer than the other major coronary arteries; the TFC for this vessel is often higher. To obtain corrected TFC for LAD coronary artery, TFC was divided by 1.7. The mean TFC for each patient and control subject was calculated by adding the TFC to LAD, CX and RCA and then dividing the obtained value into three. Due to different durations required for normal visualisation of the coronary arteries, the corrected cut-off values were 36.28±2.6 frames for LAD, 22.28±4.1 frames for CX, and 20.48±3 frames for RCA, as has been reported earlier in the literature [18]. All participants with a TFC greater than the two standard deviations of the previously published range for the particular vessel were considered to have SCF. Any values obtained above these thresholds in one of three coronary arteries (not all three) were considered to be SCF in our study. Coronary angiograms and TFC were analysed by two experienced interventional cardiologists blinded to the clinical status and laboratory measurements of the subjects.

Measurement of Tp-Te, QT and QRS Intervals from the 12-Lead ECG

All ECGs were scanned. T wave peak to end interval (Tp-Te), QT and corrected QT intervals and some other ECG intervals

were measured by an engineer with a computer program. By using a ruler, Vernier calliper or any other manual measuring tool; getting measurements off from the ECG papers could be either inaccurate or slow. Therefore ECG papers were scanned and this made it possible to gather the measurements in the digital environment. These measurements are done by a program which is generated with MATLAB (MathWorks, Natick, Massachusetts, U.S.A.) codes that written by an engineer. These codes are based on image manipulation principles.

Image manipulation method could be divided into three subdivisions: image processing, image analysis and image understanding. Image analysis is the technique that should be used to gather measurement data from ECG. Running the written code imports the image file first and then, by choice, allows user to pick points that need to be picked to get measurements or generates a matrix that consists of a dedicated numeric value of each pixel's colour. Creating a matrix gives user the flexibility of using functions which are predefined by the program. In spite of this, hand picking is easier and has a simple interface especially for beginner level users. Algorithms are developed and used to get excellent measurements in order to tolerate differences: such as tilting during scanning process, different scanning resolutions and using different ECG.

Statistical Analysis

SPSS 16.0 statistical program (SPSS Inc.; Chicago, IL, USA) was used for the statistical study. All values are given as mean±standard deviation. Mean values of continuous variables were compared between the groups using the Student t test or Mann-Whitney U test, according to whether normally distributed or not, as tested by the Kolmogorov–Smirnov test. In order to define the relationship between CSF and possible confounding factors, logistic regression analysis was used. A P value of less than 0.05 was considered significant.

Results

Evaluating the basic clinical and demographic characteristics, there was no statistically significant difference between the two groups in terms of age, gender distribution, body mass index, and smoking status and biochemical parameters except dyslipidaemia and HDL-cholesterol level (Table 1).

The TFC for all the epicardial coronary arteries, and the mean TFC, were significantly higher in the SCF group than the control group. Mean TFC of all patients with SCF was higher than that in the control group (Table 2).

Electrocardiographic parameters of the groups are shown in Table 3. QT and corrected QT were similar in CSF patients compared to the controls (357±35.2 vs 362±38.0 milliseconds and 419±25.8 vs 430±44.2 milliseconds, all p value >0.05). Tp-Te interval, Tp-Te/QT and Tp-Te/QTc ratio were significantly higher in CSF patients (85±13.7 vs 74±9.9 milliseconds and 0.24±0.03 vs 0.20±0.02 and 0.20±0.03 vs 0.17±0.02 all p value <0.001).

Table 1. Comparison of the biochemical and echocardiographic variables in coronary slow flow patients and controls

	CSF group (n=50)	Control (n=40)	p value
Age (year)	48.6±12.5	47.8±12.5	NS
Gender(male/female)	40/10	23/17	NS
BMI (kg/m^2)	28±3.5	27±3.2	NS
Smoking (%)	22 (44%)	14 (35%)	NS
Hypertension (%)	0 (0%)	0 (0%)	NS
Diabetes Mellitus (%)	3 (6%)	3 (7.5%)	NS
Dyslipidaemia (%)	19 (38%)	6 (15%)	0.029
Triglyceride (mg/dL)	190±122.3	187±94.5	NS
Glucose(fasting) (mg/dL)	102±18.6	103±22.01	NS
Creatinine (mg/dL)	0.8±0.19	0.7±0.14	NS
Total cholesterol (mg/dL)	189±48.3	179±32.2	S
HDL-*Cholesterol* (mg/dL)	41±10.4	51±14.1	0.001
LDL-*Cholesterol* (mg/dL)	108±31.8	91±24.1	NS
TSH (mIU/mL)	1.46±0.42	1.41±0.45	NS
Haemoglobin	14±1.9	13±1.5	NS
Haematocrit	42.4±5.3	42.2±4.5	NS
Heart rate (beats/min)	77±7.3	80±7.1	NS
Systolic blood pressure (mm/Hg)	120±11.7	119±13.5	NS
Diastolic blood pressure (mm/Hg)	73±8.9	74±9.6	NS
LVDD *(mm)*	46±2.4	46±1.9	NS
LVSD *(mm)*	30±2.7	29±4.8	NS
LVEF (%)	60±3.5	60±2.4	NS
LA *(mm)*	36±2.1	35±1.1	NS
E *(cm/sec)*	0.7±0.14	0.7±0.1	NS
A *(cm/sec)*	0.6±0.16	0.6±0.14	NS
E/A	1.1±0.3	1.1±0.2	NS

CSF: coronary slow flow; BMI; body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; LVEF: left ventricular ejection fraction; LA: left atrium diameter; E: early diastolic peak flow velocity; A: late diastolic peak flow velocity. Data are presented as means±SD; NS: non significant (p>0.05)

Table 2. Comparison of the TIMI frame counts in coronary slow flow patients and controls

TIMI frame count	CSF group (n=50)	Control (n=40)	p value
LAD	20±5.4	17±1.5	<0.001
Cx	24±7.8	20±2.4	=0.006
RCA	26±8.7	19±1.7	<0.001
Mean frame	23±5.04	19±1.7	<0.001

TIMI: thrombolysis in myocardial infarction; CSF: coronary slow flow; LAD: left anterior descending; Cx: circumflexy; RCA: right coronary artery. Data are presented as means±SD; NS: non significant (p>0.05)

Table 3. Comparison of the electrocardiographic features of coronary slow flow patients and controls

	CSF group (n=50)	Control (n=40)	p value
QT interval	357±35.2	362±38.0	NS
QTc interval	419±25.8	430±44.2	NS
Tp-Te interval	85±13.7	74±9.9	<0.001
Tp-Te/QT ratio	0.24±0.03	0.20±0.02	<0.001
Tp-Te/QTc ratio	0.20±0.03	0.17±0.02	<0.001

Tp-Te: T wave peak to T wave end; QTc: corrected QT. Data are presented as means±SD; NS: Non significant (p>0.05)

Discussion

The present study showed that Tp-Te interval and Tp-Te/QT ratio were prolonged in patients with CSF when compared to the control group.

The pathophysiology of CSF has not been clearly identified yet, although multiple abnormalities including inflammation, oxidative stress, endothelial dysfunction, vasculitis, platelet function disorder and atherothrombosis have been reported [19]. Increased cardiovascular morbidity and mortality have been demonstrated in patients with CSF in previous studies [8].

Recently, the Tp-Te interval and Tp-Te/QT ratio have emerged as a novel electrocardiographic markers of increased dispersion of ventricular repolarization [10, 17]. Also, these markers may be used as an electrocardiographic index of ventricular arrhythmogenesis and sudden cardiac death [10, 12]. Previous studies showed that prolongation of Tp-Te interval was associated with increased mortality in Brugada syndrome, long QT syndrome, hypertrophic cardiomyopathy, and in patients myocardial infarction [12, 14, 20].

Recently Demir et al. [21, 22] demonstrated that Tp-Te/QT ratio was significantly higher in patients with non-dipper hypertension and chronic hepatitis B.

As far as we know, there is no study available in the literature about the association between CSF and Tp-Te interval and Tp-Te/QT ratio. Kosus et al. [23] settled the data showing an increase in sympathetic tonus and decrease in vagal tonus by analysing the 24 hours Holter records in patients with SCF. Also, Yazıcı et al. [24] found higher noradrenalin and adrenalin levels in patients with SCF and suggested that increased adrenergic activity might be the manifestation of slow coronary flow. Thus, changes in autonomic neural tone may be another reason for the increase of Tp-Te interval and Tp-Te/QT ratio in patients with CSF.

Acar et al. [25] have recently found that electrocardiographic ventricular repolarization indexes are correlated with systemic inflammation. Li et al. [26] showed that the plasma concentration of inflammation markers such as high-sensitivity C-reactive protein and interleukin-6 were increased and positively correlated with TFCs in CSF patients. Recently Demir et al. [27] revealed a relationship between lower serum bilirubin concentration and CSF, because bilirubin is an important and potent endogenous antioxidant and an anti-inflammatory agent.

Inflammation may be an explanation of heterogeneity of ventricular repolarization in CSF patient but needs further investigation.

When two groups were compared in our study, QTd, Tp-Te interval and Tp-Te/QT ratio of the patients CSF were significantly higher than the control groups.

Further studies are required to determine the relation between Tp-Te interval and Tp-Te/QT ratio and ventricular arrhythmia and CSF.

We have shown for the first time that patients with CSF have higher Tp-Te interval and Tp-Te/QT ratio were compared to controls.

In conclusion, the measurement of Tp-Te interval and Tp-Te/QT ratio may be used to indicate the increased risk of CSF-related adverse cardiovascular events. According to current study findings, the risk of development of ventricular arrhythmia might be increased in CSF due to myocardial voltage gradients resulting from the heterogeneity of repolarization.

Limitations

The most important restriction of our study is the limited number of patients. Another limitation angiographic diagnosis of normal coronary arteries was based on axial contrast angiograms of the vessel lumen, which underestimates the presence of atherosclerotic plaques. Another limitation is that we did not assess the association between ventricular arrhythmias with Tp-Te interval and Tp-Te/QT ratio. Also study population could not be followed-up prospectively for ventricular arrhythmic episodes. Large-scale prospective studies are needed to determine the predictive value of prolonged Tp-Te interval and increased Tp-Te/QT ratio in this population.

Our results may contribute to pathophysiological mechanisms of the increased prevalence of ventricular arrhythmias and cardiovascular mortality risk by indicating increased ventricular repolarization heterogeneity in these patients. The increased te frequency of ventricular arrhythmia and sudden cardiac death might be explained with prolonged transmural dispersion in non-dipper patients.

In conclusion our study revealed that Tp-Te interval and Tp-Te/QT ratio were increased in CSF patients. Tp-Te interval and Tp-Te/QT ratio might be a useful marker of cardiovascular morbidity and mortality due to ventricular arrhythmias in patients with CSF.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Bursa Yuksek Ihtisas Training and Research Hospital/2013-977.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - K.K.; Design - E.T.; Supervision - F.V.A., E.T.; Funding - K.K., E.T.; Materials - B.A.; Data Collection and/or Processing - A.T.; Analysis and/or Interpretation - E.T.; Literature Review - Ö.A.O., O.C.Y.; Writing - K.K.; Critical Review - M.Y.; Other - A.T.

Acknowledgements: The authors would like to thank to Serhan Yalçınkaya M.D. for his assistance in preparing the manuscript.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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