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Evaluation of P Wave Dispersion for Prediction of Atrial Fibrillation and Corrected QT Interval Dispersion, Tp-e Interval, Tp-e/Corrected QT Ratio for Prediction of Ventricular Arrhythmic Events in Patients with Cardiac Syndrome X

Kardiyak Sendrom X'li Hastalarda Atriyal Fibrilasyon Tahmini için P Dalga Dispersiyonu, Ventriküler Aritmik Olayların Tahmin için Düzeltilmiş QT İnterval Dispersiyonu, Tp-e İnterval ve Tp-e/Düzeltilmiş QT Oranının Değerlendirilmesi

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ABSTRACT

Aim: *Even though it is well known that major adverse cardiac event rates elevate in cardiac syndrome X (CSX) patients, it is not clearly known whether the risk of atrial fibrillation (AF) and ventricular arrhythmia (VA) is elevated or not. The purpose of this study was to evaluate AF and VA risks. Therefore, P wave dispersion (PWD), an indicator of development of AF; and corrected QT interval dispersion (CQTD), Tp-e interval, Tp-e interval/corrected QT ratio, which demonstrate the risk of development of VA, were assessed in CSX patients.*
Methods: *The study was realized as a retrospective trial. A total of 298 subjects (155 CSX patients, 143 controls) were examined. PWD, CQTD, Tp-e interval, Tp-e interval/corrected QT ratio were calculated and compared between both groups.*
Results: *PWD, CQTD, Tp-e interval, Tp-e interval/corrected QT ratio values were elevated in CSX patients compared to the healthy subjects (p=0.003, p<0.001, p<0.001 and p<0.001 respectively).*
Conclusion: *Based on these outcomes it may be thought that CSX patients have increased atrial and ventricular repolarization abnormalities compared to normal population. Furthermore, our results may indirectly indicate that patients with CSX have increased risk of AF and VA.*

Keywords: *Cardiac syndrome x, electrocardiogram, repolarization anomaly*

ÖZ

Amaç: *Kardiyak sendrom X'li (KSX) hastalarda kardiyovasküler istenmeyen olayların sıklığının fazla olduğu iyi bilinmesine rağmen, atriyal fibrilasyon (AF) ve ventriküler aritmik olay riskinin artıp artmadığı net olarak bilinmemektedir. Bu çalışmanın amacı, bu riskleri değerlendirmektir. Bu amaçla AF gelişme riskini gösteren P dalga dispersiyonu (PDD) ve ventriküler aritmik olayların gelişme riskini gösteren düzeltilmiş QT interval dispersiyonu (DQTD), Tp-e interval ve Tp-e interval/düzeltilmiş QT oranı KSX'li hastalarda ölçülerek değerlendirilmiştir.*
Yöntem: *Çalışma geriye dönük olarak gerçekleştirildi. Toplam 298 birey (155 KSX'li hasta, 143 kontrol) çalışmaya dahil edildi. PDD, DQTD, Tp-e interval ve Tp-e/düzeltilmiş QT interval oranı her iki gruptada hesaplandı ve karşılaştırıldı.*
Bulgular: *PDD, DQTD, Tp-e interval ve Tp-e interval/düzeltilmiş QT interval oranı değerlerinin KSX'li hastalarda sağlıklı gruba göre istatistiksel olarak daha yüksek olduğu görüldü (p=0,003, p<0,001, p<0,001 ve p<0,001 sırasıyla).*
Sonuç: *Bu sonuçlara göre atriyal ve ventriküler repolarizasyon anormallikleri KSX'li hastalarda normal popülasyondan daha yüksek olabilir. Bu sonuçlar bize dolaylı olarak AF ve ventriküler aritmik olay sıklığının KSX'li hastalarda daha fazla olacağını düşündürebilir.*

Anahtar kelimeler: *Kardiyak sendrom x, elektrokardiyogram, repolarizasyon anomalisi*

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INTRODUCTION

Typical angina induced by exercise, abnormal noninvasive cardiac stress test results (treadmill test or myocardial perfusion scintigraphy) without any serious coronary obstruction after elimination of spontaneous or inducible coronary spasm is defined as cardiac syndrome X (CSX)[1]. Large-scale cohort studies have shown that approximately 40 percent of female patients who referred with chest pain had not any significant sign of coronary stenosis on coronary angiography, while this rate was 8 percent in male patients[2]. In these patients, the rate of other cardiovascular events for instance heart failure, sudden cardiac death (SCD) and myocardial infarction (MI) increased even though there was no serious coronary obstruction[3,4].

The difference between durations of the widest and the narrowest P-waves in a 12-derivation electrocardiogram (ECG) is defined as P wave dispersion (PWD). P wave dispersion has a well-known role in indicating atrial remodeling and predicting atrial fibrillation (AF)[5]. On the other hand the difference between the durations of the longest and the shortest QT intervals in a 12-derivation ECG is defined as QT interval dispersion (QTD). QTD has been shown to predict ventricular repolarization anomalies, ventricular arrhythmias (VA) and SCD[6]. It has been shown in recent studies that the duration between the two points where the T wave makes a peak and where it ends (Tp-e interval) has a role in indicating total dispersion and ventricular repolarization[7]. Additionally, the role of the ratio between Tp-e interval and corrected QT interval (CQT) in predicting ventricular repolarization anomalies and ventricular arrhythmias is well known[8].

Even though it is well known that major adverse cardiac event rates elevate in CSX patients, it is not clear whether the risk of AF and VA is elevated or not. The purpose for the present study was to assess AF and VA risks in these patients. Therefore, PWD a predictor of AF; and CQTD, Top-e interval, Top-e interval/corrected QT ratio , which are indicators of VA, were assessed in CSX patients.

MATERIAL and METHODS

This cross-sectional, observational study was conducted retrospectively. We reviewed the medical records of subjects who experienced coronary angiographies (CAG) in Baskent University, Adana Hospital between January 1st, 2012 and October 31st, 2017. A total of 155 patients (97 female, 58 male) with CSX diagnosed without any sign of significant coronary stenosis on coronary angiography were included into the study. A total of 143 healthy volunteers (95 female, 48 male) were included in the control group. These subjects had a negative treadmill test and normal coronary computed tomography findings. ECGs of all individuals in both groups were recorded. PWD, CQT dispersion (CQTD), Top-e and Top-e/CQT ratio were calculated and compared between the groups. Then Duke Treadmill scores of patients with CSX were calculated. It was investigated whether there was a correlation between these ECG parameters and Duke Treadmill scores.

CSX was determined according to 4 criteria. These criteria were;

1. Typical angina induced by exercise
2. Transient ST segment depression (> 1 mm), during the tread mill test
3. No serious coronary artery obstruction on coronary angiography
4. Exclusion of coronary vasospasm with a provocation test.

Exclusion criteria of the study included presence of known atherosclerotic cardiovascular disease (ASCVD) (including coronary ecstasies and plaque), diabetes mellitus, malignancy, hypertension, smoking, heart failure (EF<%40), moderate or advanced heart valve disease, permanent pacemaker, pregnancy, patients who have not adequate heart rate response during the treadmill test or the test is non-diagnostic, presence of active infection, end stage kidney disease, chronic end-stage hepatic disorders, autoimmune diseases requiring systemic steroids, chronic pulmonary disorders. Patients who were on the medications which may affect CQT such as macrolides, amiodarone, sotalol, etc.) were also excluded.

Treadmill Exercise Test

Treadmill test of all patients was performed according to modified Bruce protocol[9]. All patients were fasted for 4 hours as a standard protocol prior to the test. All drugs that affecting heart rate was discontinued 72 hours before the exercise test. The test was accepted as diagnostic if no less than 85 percent of the heart rate adjusted by age (220-years) was reached. During the exercise test, a three-stage protocol was applied, each of which lasted for 3 minutes, and the slope and speed of the treadmill gradually increased[10]. The test was stopped when the age-targeted heart rate reached 95 percent or when the patient wanted to stop the test. Duke treadmill test scores (DTS) of all patients were calculated and recorded (DTS=Exercise Time - (5 x Max ST) - (4 x Angina index)). In this the parametres are defined a follows: max ST; maximum net ST deviation (aVR except), angina index; 0=no angina during the test, 1=non-limiting angina, 2=exercise limited angina. Duke tread mill score of ≥5 was considered as low, and ≤ -11 as high risk for coronary artery disease[11].

Imaging of coronary arteries

Patients underwent coronary angiography by using the modified Seldinger technique via the femoral or radial artery. Coronary arteries were demonstrated at standard projections as described before. In order to exclude coronary spasm, hyperventilation test was used. Normal coronary arteries were defined as the absence of any luminal narrowing. Two-experienced blinded invasive cardiologists reviewed all the angiographic data of patients. Images were reevaluated, if necessary.

Electrocardiographic features

We retrospectively reviewed standard ECG (25 mm/s and 10 mm/mV)[12]. All ECG recordings were scanned and recorded in digital media. The images were magnified 400x using Adobe Photoshop software in order to minimize errors during measurements. Two separate operators who were blinded to the patient and control groups calculated all ECG parameters. For each parameter, measurements were made from three consecutive beats in every derivation, and the average of these measurements was recorded. PWD was measured by calculating the difference between the durations of the widest and the narrowest P waves in the ECG. QT interval was measured as the interval between the onset of the Q wave and the end of the T wave. Corrected QT was calculated using Bazett's formula: CQT=QTV (R–R interval). Tp-e interval was measured in precordial leads by calculating the interval between the point where the T wave makes a peak and where it ends. Tp-e/CQT ratio was figured from these parameters.

Statistical analyses

All parameters were evaluated by the SPSS software (SPSS version 21.0; SPSS Inc., Chicago, IL, USA). Continuous variables were tested for normal distribution by using Kolmogorov-Smirnov test. The results including normally distributed variables were expressed as mean ± standard deviation while non-normally distributed variables were expressed as medians and interquartile ranges. Categorical variables were shown as absolute value and the percentage. Independent samples t-test was used to compare the two groups with respect to the variables with normal distribution and homogeneous group variance. Variables that showed a non-homogenous distribution were compared by the Mann Whitney U test. Categorical variables such as clinical characteristics of the groups were compared with chi-square test. Spearman's or Pearson correlation tests were used to find out the degrees of association between continuous variables. A $p<0.05$ was considered as statistically significant.

Ethical Approval: The local ethics committee approved the study (Başkent University Ethics Committee, Date: 12th September, 2017, Number: 31714).

RESULTS

Our study included 298 individuals (155 patients

with CSX and 143 control). Table 1 shows baseline clinical and demographic features of the 2 groups, there were no differences between the 2 groups regarding baseline clinical features (p>0.05). The mean PWD were found to be 34.8±12.54 msn in the control, and 39.18±12.46 msn in the CSX group and this difference was statistically significant (p=0.003). Similarly when we compared CQTD values we found a statistically significant difference between the groups (46.62±11.88 msn vs. 52.27±13.78 msn, p<0.001). T wave peak-end interval values we found were 70.44±8.15 msn in the control, and 73.68±7.63 msn in the CSX group. There was a statistically significant difference between the groups in terms of Tp-e interval (p<0.001). Similarly Tp-e/CQT ratio was found to be 0.18±0.01 in the control and 0.19±0.01 in the CSX group, and the difference was statistically significant (p<0.001). The PWD, CQTD, Tp-e interval and Tp-e/CQT ratios of the groups, and their comparisons are shown in Table 2.

Table 1. Baseline clinical characteristics of the study population.

Variables	Patients (n=155)	Control (n=143)	p
Age (years)	59.35±9.35	59.17±10.87	0.878
Female gender, n (%)	97 (62.58)	95 (66.43)	0.488
EF (%)	55.24±3.17	54.79±3.78	0.261
Creatinine (mg/dL)	0.75±0.12	0.75±0.12	0.964
Hb (mg/dL)	13.9±1.4	14.01±1.16	0.488
WBC (/mm^3)	7469±2171	7153±1658	0.161
Platelets (100/mm^3)	269 (228-303, IQR=75)	239 (223-301, IQR=78)	0.396
FPG (mg/dL)	100.75±12.16	105.03±10.75	0.586
TC (mg/dL)	217.93±38.01	211.23±36.68	0.123
HDL (mg/dL)	46.11±8.92	47.08±7.51	0.315
LDL (mg/dL)	133.19±30.66	127.73±35.91	0.158
Triglyceride (mg/dL)	136 (109-169, IQR=60)	125 (85-191, IQR=106)	0.286
Potassium (mEq/L)	4.28±0.49	4.22±0.44	0.302

EF: Ejection fraction, FPG: Fasting plasma glucose, Hb: Hemoglobin, HDL: High density lipoprotein, HL: Hyperlipidemia, IQR: Interquartile range, TC: Total cholesterol, WBC: White blood cell.

Table 2. Comparison of P wave dispersion, corrected QT interval dispersion, Tp-e interval, Tp-e/corrected QT ratio between the patients with cardiac syndrome x and control group.

	Patients (n=155)	Control (n=143)	p
PWD	39.18±12.46	34.8±12.54	<0.05
CQTD	52.27±13.78	46.62±11.88	<0.001
Tp-e	73.68±7.63	70.44±8.15	<0.001
Tp-e/CQT	0.19±0.01	0.18±0.01	<0.001

CQT: Corrected QT interval, CQTD: Corrected QT interval dispersion, PWD: P wave dispersion, Tp-e: T wave peak and end interval.

When we performed correlation analyses we found that PWD, CQTD, Tp-e and Tp-e/CQT ratio were negatively correlated with Duke treadmill scores (r=-0.605, p<0.001, r=-0.619, p<0.001, r=-0.317, p<0.001 and r= -0.405, p<0.001, respectively). Results of the correlation analysis of PWD, CQTD, Tp-e, Tp-e/CQT proportion and Duke treadmill score are shown in Figure 1.

DISCUSSION

Our study is the first study in the literature investigating PWD, CQTD, Tp-e and Tp-e / CQT in patients with CSX. According to the results of our study, in patients with CSX, these ECG parameters were significantly higher than in the normal population. We suggest that CSX patients have increased atrial and ventricular repolarization abnormalities compared to normal population. Furthermore, our results may indirectly indicate that patients with CSX have increased risks of AF and VA.

In the literature, there are no large-scale randomized controlled trials investigating AF frequency in patients with CSX. Altun et al.[13] found that the PWD was higher than the normal population in their study of 21 patients with CSX. In patients with CSX, there may be some reasons for the high risk of developing AF. The etiologic factors in CSX are usually coronary microvascular dysfunction and microvascular angina. Skalidis et al.[14] investigated 16 recurrent lone AF patients. In this study, coronary flow velocities of patients were measured after coronary angiography and compared with those of the healthy population. In conclusion, it has been shown that atrial perfusion is impaired in recurrent lone AF patients and have come to the conclusion that coronary microvascular dysfunction may cause this condition. Another common mechanism that plays a role in the pathophysi-

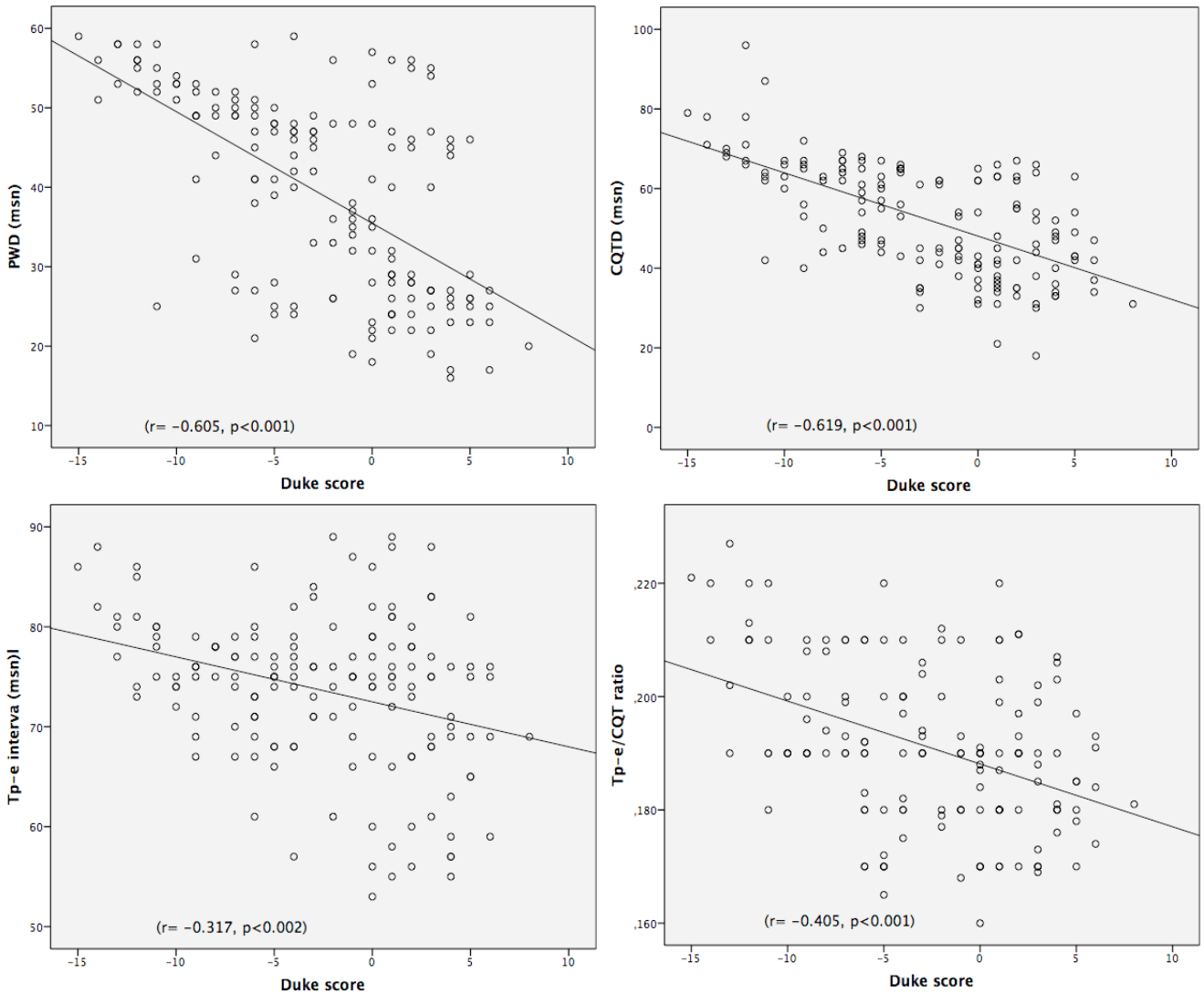

Figure 1. Correlation analysis between PWD, CQTD, Tp-e interval, Tp-e/CQT ratio and Duke treadmill score.

ology of both diseases is inflammation. In another study conducted by Demir et al.[15] serum levels of interleukin-6 and interleukin-10, a proinflammatory substance, were found to be higher in patients with CSX and serum TNF-a level, which is an anti-inflammatory substance, is found to be lower than normal population. Similarly, the role of inflammation in the development of AF is well known and has been shown in many studies[16,18].

According to another result of our study, In ECG, some parameters showing risks of ventricular repolarization abnormalities and ventricular arrhythmia were higher in patients with CSX. In the literature, there are no large-scale randomized controlled trials investigating ventricular arrhythmia in CSX patients. A study by Sara et al.[19] found that the duration of CQT in patients with coronary angiography without significant coronary stenosis but with coronary microvascular dysfunction were higher than patients without microvascular dysfunction. In another study conducted by Lutfi et al.[20] patients with CSX and severe coronary stenosis when compared with ventricular repolarization. As a result of the study, they concluded that the risk of ventricular repolarization abnormality might be similar in these two groups of patients. In

patients with CSX, there can be a variety of reasons for repolarization abnormalities. In coronary microvascular dysfunction, which is mostly caused by CSX, there is increased sensitivity and/or inadequate relaxation after vasoconstriction in prearterioles and intramural arterioles[1,3,9]. As a result, the impaired blood flow, ischemia and angina develop in ventricular myocardium. It is well known that ischemia causes ventricular repolarization disorder and triggers ventricular arrhythmias[21]. Increased ischemia and angina may have led to repolarization abnormalities in CSX patients. It is demonstrated in large scale studies that Tp-e interval might be a useful index to predict ventricular tachyarrhythmia and cardiovascular mortality[22-25]. Another result of our study was negative correlation between DTS and CQTD, Tp-e, Tp-e/CQT ratio. The role of DTS in ischemia has been demonstrated in previous studies[26,27]. This negative correlation in the results supports that the cause of repolarization abnormality in CSX patients may be ischemia and angina.

Limitations of the study: In our study, AF and ventricular arrhythmia were not evaluated directly, instead the markers of these arrhythmias were evaluated. There may have been silent arrhythmias not felt by the patient and not recognized by the clinician. The study was performed retrospectively and it is not clear how the outcome of these patients will be in long-term follow-ups. Repeatability and reliability are the most important problems in operator-dependent measurements. To solve this problem, EKGs were enlarged x400 times in digital environment and two different cardiologists made two measurements. Although there were no significant differences between the groups as for potassium levels, unfortunately due to the lack of data, magnesium levels could not be compared between the groups.

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