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Relation Between Index of Cardio-Electrophysiological Balance and Tp-e/QT Ratio and Coranary Collateral Circulation

Kardiyak Elektrofizyolojik Denge İndeksi ve Tp-e/QT Oranı ile Koroner Kollateral Dolaşım Arasındaki İlişki

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Öz

Amaç: QT intervali / QRS süresi olarak hesaplanan kardiyak elektrofizyolojik denge indeksi (iCEB), malign ventriküler aritmileri öngörmek için yeni bir gösterge olarak tanımlanmıştır. Burada, koroner kollateral dolaşım (KKD) derecesinin; iCEB ve Tp-e / QT oranı ile ilişkisini araştırmayı amaçladık.
Hastalar ve Yöntem: Kronik total oklüzyon (KTO) tanısı olan 44 hasta ile benzer yaş ve cinsiyet dağılımında 55 sağlıklı kişi çalışmaya alındı. KTO hastaları, iyi (n = 24) ve zayıf (n = 20) kollateral grubu olarak sınıflandırıldı. Tüm hastaların 12-lead standart elektrokardiyogramı (EKG) kaydedildi ve Tp-e aralığı, QT aralığı, QRS süresi, Tp-e/QT oranı ve QT/QRS oranları ölçüldü.
Bulgular: Ortalama Tp-e aralığı ve Tp-e/QT oranı gruplar arasında benzerdi. Ayrıca, gruplar arasında iCEB veya iCEBc değerleri benzer izlendi. Alt grup analizinde, KKD derecesi ile Tp-e/QT oranı, Tp-e süresi ve QT/QRS oranını içeren EKG parametreleri arasında bir ilişki saptanmadı.
Sonuç: KTO'lu hastalarda iCEB ve Tp-e/QT oranı ile KKD gelişiminin derecesi arasında anlamlı bir ilişki saptanmadı.

Anahtar Kelimeler: Aritmi, iCEB, kollateral, kronik total tıkanıklık, QT/QRS oranı

Abstract

Aim: Index of cardiac electrophysiological balance (iCEB), calculated as QT interval / QRS duration, has been described as a novel indicator for predicting malignant ventricular arrhythmias. Herein, we aimed to explore the relation of coronary collateral circulation (CCC) degree with iCEB and Tp-e / QT ratio.
Patient and Methods: Forty-four patients diagnosed with chronic total occlusion (CTO) and 55 healthy subjects in comparable age and sex distribution were included. We classified the CTO patients as good (n= 24) and poor (n= 20) collateral groups. Standard 12-lead standard electrocardiogram (ECG) of all patients was recorded and Tp-Te interval, QT interval, QRS duration, Tp-Te/QT ratio and QT/QRS ratio were measured.
Results: Mean Tp-e interval and Tp-e/QT ratio were similar between groups. Also, the groups were comparable regarding iCEB or iCEBc values. In subgroup analysis, there was no relationship between the degree of CCC and ECG parameters including Tp-e/QT ratio, Tp-e and QT/QRS ratio.
Conclusion: There was no significant relationship between the iCEB and Tp-e/QT ratio, and the degree of CCC development in patients having CTO.

Key words: arrhythmia, chronic total occlusion, collateral, iCEB, QT/QRS ratio

INTRODUCTION

Cardiac arrhythmias are known as the leading cause of mortality in patients with coronary artery disease (CAD) (1). Myocardial ischemia is considered as the major pathological reason for most of the sudden cardiac death (SCD) cases resulting from malignant ventricular arrhythmias (2). At this point, coronary collateral circulation (CCC) development in case of chronic ischemia can be regarded as an adaptation mechanism improved by the heart to protect itself. Previous studies have demonstrated that well-developed coronary collaterals in CAD patients play a protective role to diminish the major adverse cardiac event risk, even cardiac mortality, and all cause deaths (3, 4).

Standart surface electrocardiogram (ECG) is a simple and commonly used diagnostic tool that shows electrical myocardial changes during ischaemia. Herein, QT interval prolongation is the most known ECG finding that is a marker for electrical instability and SCD (5). Previously, Meier et al. (6) have demonstrated that well-developed CCC has a positive effect against cardiac death via reducing the QT prolongation occurs during early phase of ischemia.

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Moreover, the interval from peak to the end of T wave (Tp-e) and Tp-e/QT ratio on 12-lead surface ECG are novel proarrhythmogenic markers which give an idea about transmural dispersion of left ventricular (LV) repolarization (7, 8). Also, Tp-e interval and Tp-e/QT ratio have been found lower in the patients who have well developed CCC compared to those with poor CCC development (9).

iCEB, formulized as QT interval / QRS duration, has been identified as a new proarrhythmogenic risk cursor for predicting ventricular arrhythmias (10). It has been shown that increased levels of iCEB predict torsades de pointes (TdP) while decreased levels of iCEB predict non-torsades de pointes mediated ventricular tachycardia or ventricular fibrillation (11). There is little data in the literature about the clinical usefullness of iCEB for the risk prediction of the patients regarding ventricular arrhythmias (12, 13). So, the aim of this study was to investigate the impact of CCC development on ventricular arrhythmia indexes based on iCEB, Tp-e and Tp-e/QT ratio in stable CAD patients.

PATIENT AND METHODS

Study design

This study was designed as a cross-sectional study which included ninety nine consecutive patients who underwent elective coronary angiography because of clinical symptoms or after a positive non-invasive cardiac test (positive cardiac stress test, ischemia in myocardial perfusion scintigraphy, patients with recently detected LV wall motion abnormalities, or patients with stable angina pectoris, etc.) in our department between June 2017 and May 2018. The patients who had chronic renal disease or electrolyte hemoastatis disorders, acute or chronic inflammatory disease, an active malignancy, and those receiving any drugs that may affect cardiac conduction (antiarrhythmic drugs, digitalis, β-blocker, or nondihydropyridine calcium channel blockers medication, any kind of theraphy for chronic obstructive pulmonary disease), those with a history of myocardial infarction or coronary revascularization (via coronary artery bypass graft operation or percutaneous coronary intervention), those with documented atrial fibrillation (AF), permanent cardiac pacemaker implantation, sick sinus syndrome, any kind of bundle branch blocks, pre-excitation syndromes, atrioventricular block, LV hypertrophy and valvular heart disease (moderate-to-severe) were excluded from the study. Demographic characteristics, cardiovascular risk factors and routine hematological and biochemical test results were noted. An informed consent was taken from all participants. The study was approved by the Local Ethics Committee (Necmettin Erbakan University, Meram Medical Faculty 2018/1411).

Coronary angiography and scoring of coronary collateral circulation.

Selective invasive coronary angiography was performed via the right femoral artery, if appropriate, using the standart Judkins technique. Two interventional cardiologists evaluated the coronary angiograms together with the level of CCC development and they were blinded to patients' clinical information. The degree of distal vessel filling by CCC was classified according to the Rentrop and Cohen method as following; Grade 0, no filling of any collateral; Grade 1, poorly filling of side branches by collateral vessels without viewing the epicardial segment; Grade 2, partial filling of the epicardial coronary artery by collateral vessels; Grade 3, complete filling of the major epicardial coronary artery by collateral vessels (14). In case of more than one occluded vessel, the best collateral filling was accepted for the classification of patient's collateral status. The CTO was defined as a total occlusion in an epicardial coronary artery for more than three months with total blocking of antegrade blood flow on coronary angiograms (15). Patients who have grades 0 or 1 CCC were included in the 'poor CCC group' (n= 20); while those having grade 2 or 3 CCC formed the 'well CCC group' (n= 24). And 55 healthy subjects with normal coronary anatomy were included to the study as control group.

Evaluation of electrocardiographic parameters

The standart 12-lead surface ECGs of patients were recorded following at least one hour of resting period (10 mV/mm and 25 mm/s paper speed; Marquette Case, Hellige Medical System, Cardiosmart Hellige Instrument Company, Freiburg, Germany). QT interval, QRS duration, T wave, Tpeak-Tend interval and heart rate were noted. All of the ECG examples were sent to a digital platform to decrease the margin of error during measurement, and then a software (Adobe Photoshop) was used for magnification.

On the chest leads, the measurement of Tp-e interval was performed between the peak point to the end of T wave (16, 17). On surface ECG, the QT interval was accepted between the begining of QRS complex and the ending point of the T-wave. Then we calculated the 'corrected QT interval' (cQT) with

the Bazett formula: cQT = QT√(R–R interval). Leads II and V5 were used to measure QT interval. We used the longest measurement in statistical analysis (17). The Tp-e/QT ratio was defined as ratio of Tp-e duration in lead V5 to the QT interval in the same lead. We excluded the patients who had U waves on surface ECG. iCEB was calculated as QT interval / QRS duration (on lead 2 or V5) in the same leads.

Statistical analysis

We used SSPS® version 16.0 statistical package program (SPSS Inc., Chicago, IL, United States) for statistical analyses. We presented the quantitative variables fitting into normal distribution given as mean ± standard deviation while we presented the categorical variables as number and percentages. Normality of distribution was evaluated using the Kolmogorov–Smirnov test. The Student t-test was used to compare two independent groups in terms of the means of normally distributed numerical variables. One way ANOVA test, or Kruskal-Wallis test were used in comparisons of more than 2 independent groups, if normally distributed, or not, respectively. The chi-square test was performed to compare the study groups in terms of categorical variables. A p value below 0.05 was considered as statistically significant.

RESULTS

A total of 99 patients with a mean age of 62.73±9.95 years, 49 (49.5%) of whom were women, formed the study population. There was no statistically significant difference between coronary colletaral group and the control group in terms of gender, age, serum lipid profile and body mass index (BMI). Also, we did not detect a statistically significant difference between groups regarding percentage of smokers, presence of diabetes mellitus or hypertension, and laboratory measurements. The study groups were comparable in terms of heart rate on ECG, QRS duration, QT interval and QTc values. Tp-e intervals and Tp-e/QT ratio were also similar between groups (p=0.83 and p=0.93, respectively). iCEB or iCEBc values were not different between groups (p=0.98 and p=0.36, respectively). The demographic features, laboratory parameters, electrocardiographic characteristics and comparison between coronary colletaral group and healty subjects of the study population are

Table 1. Demographic, clinical and laboratory characteristics of study population

	Control group (n= 55)	Collateral group (n= 44)	p value
Age (years)	61.6±8.8	64.1±11.2	0.23
BMI (kg/m2)	27.8±4.8	27.6±4.0	0.75
Sex (female), n(%)	28(50.9)	22(50)	0.92
DM, n(%)	18(32.7)	18(40.9)	0.40
Hypertension, n(%)	28(50.9)	24(54.5)	0.71
Smoking, n(%)	16(29.1)	18(40.9)	0.21
LVEF (%)	54.7±7.4	54.3±5.7	0.77
Creatinine (mg/dl)	0.78±0.19	0.84±0.14	0.07
Hb (g/dl)	13.8±1.6	13.7±1.7	0.84
Platelet (103/mm^3)	263.4±77.3	248.3±73.1	0.15
Leukocyte(103/mm^3)	7.65±1.7	7.68±1.3	0.91
FBG (mg/dl)	97(87-121)	102(90-113)	0.53
Total cholesterol (mg/dl)	201.8±43.8	192.4±46.3	0.25
LDL-C (mg/dl)	123.6±36.7	110.4±49.1	0.13
HDL-C (mg/dl)	47.9±12.9	44.4±7.1	0.11
Triglyceride (mg/dl)	155.0±97.6	160.7±91.6	0.73
Electrocardiographical Findings			
Heart rate (bpm)	71.9±12.1	77.0±17.8	0.11
QT interval (ms)	379.9±34.3	384.2±42.3	0.54
QTc interval (ms)	421.3±34.6	423.1±38.1	0.78
QRS interval (ms)	88.4±18.0	86.4±13.5	0.52
Tp-e interval (ms)	78.5±19.2	77.7±18.9	0.83
Tp-e/QT ratio	0.20±0.05	0.20±0.70	0.93
iCEB (QT/QRS)	4.53±0.83	4.53±0.7	0.98
iCEBc (QTcB/QRS)	4.92±0.84	5.07±0.79	0.36

* BMI, Body Mass Index; CTO, chronic totally oclusion; DM, diabetes mellitus; FBG, fasting plasma glucose; Hb, hemoglobin; HDL-C, high-density lipoprotein cholesterol; iCEB, index of cardio-electrophysiological balance; iCEBc, corrected index of cardio-electrophysiological balance; LDL-C, low-density lipoprotein cholesterol; LVEF, Left ventricular ejection fraction

Table 2. Demographic, clinical and laboratory characteristics according to coronary collateral circulation

	Poor CCC (n= 20)	Well CCC (n= 24)	p value
Age (years)	62.4±10.7	65.4±11.6	0.37
BMI (kg/m2)	27.5±4.6	27.7±3.6	0.87
Sex (female), n(%)	11(55)	11 (45.8)	0.54
DM, n(%)	9 (45)	9 (37.5)	0.61
Hypertension, n(%)	11 (55)	13 (54.2)	0.95
Smoking, n(%)	7 (35)	11 (45.8)	0.46
LVEF (%)	55.4±5.8	53.4±5.5	0.26
Creatinine (mg/dl)	0.85±0.15	0.84±0.13	0.68
Hb (g/dl)	13.5±1.4	14.0±1.8	0.12
Platelet (103/mm3)	263.4±77.3	248.3±73.1	0.15
Leukocyte(103/mm3)	7.50±1.4	7.85±1.3	0.39
FBG (mg/dl)	97(87-121)	102(90-113)	0.53
Total cholesterol (mg/dl)	201.8±43.8	192.4±46.3	0.25
LDL-C (mg/dl)	104.7±31.2	115.0±60.2	0.06
HDL-C (mg/dl)	43.4±8.0	45.1±6.4	0.67
Triglyceride (mg/dl)	155.0±97.6	160.7±91.6	0.73
Electrocardiography Findings			
Heart rate (bpm)	80.2±17.7	74.5±17.8	0.29
QT interval (ms)	379.9±34.3	384.2±42.3	0.54
QTc interval (ms)	421.3±34.6	423.1±38.1	0.78
QRS interval (ms)	87.3±15.3	85.6±12.1	0.69
Tp-e interval (ms)	76.0±16.7	79.1±20.8	0.58
Tp-e/QT ratio	0.20±0.04	0.20±0.04	0.89
iCEB (QT/QRS)	4.43±0.75	4.61±0.65	0.40
iCEBc (QTcB/QRS)	5.06±0.90	5.08±0.71	0.94

* BMI, Body Mass Index;CCC, coronary colletaral circulation; CTO, chronic totally oclusion; DM, diabetes mellitus; FBG, fasting plasma glucose; Hb, hemoglobin; HDL-C, high-density lipoprotein cholesterol; iCEB, index of cardio-electrophysiological balance; iCEBc, corrected index of cardio-electrophysiological balance; LDL-C, low-density lipoprotein cholesterol; LVEF, Left ventricular ejection fraction

summarized in Table 1.

In subgroup analysis, we did not find any relationship between the degree of CCC and ECG parameters including Tp-e/QT ratio, Tp-e and iCEB (p=0.89, p=0.58 and p=0.40, respectively). Table 2 demonstrates the electrocardiographic parameters, demographic characteristics and comparison of well and poor collateral groups.

DISCUSSION

In the current study, our results indicate that Tp-e, Tp-e / QT ratio or QT / QRS ratio on standard 12-lead surface ECG were not good predictors of CCC development in patients with CTO. Moreover, the results of this study did not suggest any relationship between cardiac electrophysiological balance and the degree of CCC development. Therefore, it is not possible to mention the usefullness of iCEB as a predictor of malignant ventricular tachyarrhythmias in CAD patients with CTO.

The presence and extent of ischemia in myocardial tissue has been reported as a major risk factor for ventricular tachyarrhythmias in stable CAD patients. Development of CCC can be considered as an adaptive mechanism in chronic myocardial ischemia. Previous studies have demonstrated that good CCC development can contribute in decreasing the number of ischemic events, minimize myocardial infarct size and prolong survival in patients with CAD (3, 18, 19). However, there is still no consensus to explain the protective mechanism of CCC development on ventricular tachyarrhythmias in stable CAD patients. Ohkita et al. stated that partial perfusion via collateral vessels during severe ischemia was not enough to prevent VF development (20). On the other hand, a number of previous studies speculate that the presence of well developed CCC in cases with CAD may elevate the threshold of malignant arrhythmias and lowers the risk of fatal arrhythmias (4, 21, 22). Yano K et al. have demonstrated that diminished collateral blood flow results in more heterogeneous refractory period and conduction delay in the preexisting ischemic myocardium, which may increase vulnerability to fatal ventricular arrhythmias

(23). In this context, several parameters and intervals have been described on surface ECG to determine the arrhythmogenic risks.

It is well known that fragmented QRS (fQRS) on any derivation of 12-lead surface electrocardiogram (ECG) is associated with territorial myocardial scar and consequent ventricular arrhythmias (24, 25). Kadi H et al. (26) speculated that the presence of fQRS on surface ECG may indicate poorly developed CCC in CAD patients having chronic total occlusion. QT dispersion on surface ECG shows the heterogenity of ventricular repolarization which is associated ventricular arryhtmias. And Tandogan I et al. (27) demonstrated that corrected QT dispersion tends to be greater in CAD patients who have well developed CCC than those with poor CCC development. Pascal M et al. (6) demonstrated the QT prolongation during balloon occlusion in left anterior descending (LAD) and circumflex (Cx) coronary artery, but not for the right coronary artery (RCA). Some previous studies have proposed an association between Tp-e interval and Tp-e/QT ratio with SCD, which indicates the transmural dispersion of ventricular repolarization (28). Tasolar H et al. (9). have shown that patients with well developed collaterals have shorter Tp-e interval and lower Tp-e/QT ratio are compared to those with poor CCC. Cetin M et al. (29) demonstrated that Tp-e, the Tp-e/QT ratio, and QTc dispersion have substantially decreased after succesful revascularization of the CTO lesion by percutaneous coronary intervention compared to those measured before revascularization. In our study, we did not detect a relationship between these ECG parameters and the degree of CCC development. In our study population, 52.3% of them had total occlusion in Cx artery, 20.5% in LAD artery, and 13.6% in RCA. The difference in the distribution of coronary artery dominance among the patients may be the main cause of this result. This situation may also be the result of a small area of affected myocardial tissues. And also, the fact that the ejection fractions of the patients are close to normal ranges may also have an effect.

Recently, a novel non-invasive marker named iCEB, formulated as QT interval / QRS duration, was defined as a potential risk indicator for drug-induced ventricular arrhythmias in an experimental animal model (10). Moreover, it has been demonstrated that iCEB is correlated with the cardiac wavelength λ (λ = effective refractory period (ERP) x conduction velocity) and that any increase or decrease in iCEB might probably be related with TdP or non-TdP mediated VT/VF, respectively (10, 11). Previously, the association between malignant ventricular arryhtmias and cardiac wavelength λ was well described (30). Therefore, Robyns T et al. (11) as a result of their human study spaculated that iCEB may be a noninvasive and easy to measure marker of increased arrhythmogenesis considering that the iCEB is equivelant of cardiac wave length.

Based on these findings, Yumurtacı O et al. (12) found that iCEB and heart rate-corrected QT(QTc)/QRS ratio was higher in patients with acute myocarditis who had ventricular arrhythmic episodes compared to uneventful control group. Recently, Ucar FM et al. (13) have investigated the balance of ventricular depolarization and repolarization in rheumatoid arthritis patients by using iCEB. They found that iCEB (QT/QRS) was higher in patients with rheumatoid arthritis than in healthy subjects. Moreover, they have found a positive correlation between iCEB and hsCRP levels. Finally, they speculated that increased frequency of SCD resulting from malignant ventricular tachyarrhythmias in rheumatoid arthritis patients may be TdP-related and this potential relationship can be explained by recently defined index of balance between depolarization and repolarization (13). Studies have also shown that higher iCEB is associated with higher pericardial fat volume which is related with subclinical atherosclerosis and increased inflammatory response and AF or other cardiac conduction problems (31, 32). But interestingly, Nafakhi H et al. (31) have not found a statistically significant relationship between iCEB and coronary artery calcification values. Similarly, Tp-e/QT ratio was in parallel with iCEB where higher values were useful in predicting ventricular arrhythmias in myocarditis, rheumatoid arthritis and thicker pericardial fat tissue in the studies mentioned above.

This study have some limitations. Firstly, relatively small sample size of our study is a limitation. Since electrophysiological study (EPS) is an invasive procedure, we could not perform to our study population routinely for research purposes. The absence of simultaneous EPS of the subject included is another limitation. Coronary dominance might also be analyzed with coronary computed tomography angiography. The results might change after myocardial viability scan or ischemic area detection.

CONCLUSION

Finally, our finding indicates that QT/QRS (iCEB)

measurement, which is readily available from 12-lead surface ECG, is not different between CAD patients having chronic total occlusion and healty subjects. It also has not changed with respect to the degree of coronary collateral flow. Further large scale, randomized, prospective, long-term follow-up studies are necessary to clarify the role of iCEB in predicting ventricular arrhythmias and/or SCD.

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