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Evaluation of Index of Cardioelectrophysiological Balance (iCEB) in Patients with Rheumatoid Arthritis

ORIGINAL ARTICLE

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ABSTRACT

Objective: Index of cardioelectrophysiological balance (iCEB), measured as QT interval divided by QRS duration, is defined recently as a new risk marker for arrhythmias. Increased or decreased iCEB is associated with malignant ventricular arrhythmias. We aimed to investigate the ventricular balance between the depolarization (changes in QRS duration) and repolarization (changes in the QT interval) of the cardiac action potential in rheumatoid arthritis (RA) patients by using iCEB.

Materials and Methods: In total, 60 patients (mean age was 49.4±11.7 y and 61% of the patients were female) with RA and 60 control subjects (45.3±12.6 y and 60% of the patients were female) were enrolled. iCEB (QT/QRS) and iCEBc [heart rate-corrected QT (QTc)/QRS] rates were calculated from the 12-lead electrocardiogram.

Results: iCEB and iCEBc were significantly higher in patients with RA than in control subjects ($p<0.001$ and $p<0.001$, respectively), and they were correlated with high-sensitivity C-reactive protein (hsCRP) levels ($r=0.467$, $p<0.001$ and $r=0.479$, $p<0.001$, respectively)

Conclusions: Our results indicate that iCEB was increased in patients with RA. It is known that high iCEB is associated with torsade de Pointes (TdP) ventricular tachycardia. The increased frequency of ventricular arrhythmias in patients with RA may be TdP-related and can be clarified by the new index of balance between depolarization and repolarization (iCEB).

Keywords: Index of cardioelectrophysiological balance, rheumatoid arthritis, sudden cardiac death

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease related with increased risk of cardiovascular disease and premature mortality (1, 2). Cardiovascular diseases are the main cause of about a half of the premature deaths in these patients (2). Sudden cardiac death (SCD) risk in patients with RA is two times higher than in non-RA subjects (3).

Repolarization heterogeneities on electrocardiography (ECG) are related to malign arrhythmias and SCD (4). QT dispersion, which is a marker of repolarization heterogeneity, has been found longer and associated with increased mortality in patients with RA (5). T peak-to-end (Tp-e-the interval between the peak and the end of the T wave on electrocardiogram-and Tp-e/QT ratio are electrocardiographic indexes of total dispersion of ventricular repolarization (6, 7) and an increase in these parameters has also been reported in patients with RA (8).

A new non-invasive marker-index of cardioelectrophysiological balance (iCEB) between the depolarization and repolarization of the action potential-was defined as a potential risk predictor of arrhythmia in an animal study (9). iCEB is measured as QT interval divided by QRS interval on surface ECG. iCEB is equivalent to the cardiac wavelength, which can be measured invasively with electrophysiological study and plays an important role in arrhythmogenesis (10). To the best of our knowledge till date, no study has evaluated the iCEB as a marker of ventricular arrhythmogenesis in patients with RA. Therefore, in this study, we aimed to assess the balance of ventricular depolarization and repolarization in patients with RA by using iCEB.

MATERIALS and METHODS

Study population

The present study is a single-centered study, based on a retrospective analysis of the data collected between January 2015 and May 2016 from 60 consecutive patients with RA and prospective analysis of 60 age- and sex-matched control subjects. All patients conformed to the American Rheumatism Association criteria (1987) for RA (11). The study was approved by the local ethics committee and was implemented in complete concordance with the Declaration of Helsinki on human research.

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Table 1. Baseline demographic, clinical characteristics, and laboratory parameters of the study subjects

	Rheumatoid Arthritis Patients (n=60)	Control Subjects (n=60)	p
Female (%,n)	61% (37)	60% (36)	0.85
Age	49.4±11.7	45.3±12.6	0.06
Hyperlipidemia (%,n)	5% (3)	3.3% (2)	0.64
Smoking (%,n)	3% (2)	8% (5)	0.24
Body Mass index	25.6±1.9	26.5±3.0	0.06
Systolic Blood Pressure(mmHG)	127±5.9	125±8.0	0.07
Diastolic Blood Pressure (mmHG)	79±5.6	77±8.4	0.06
Glucose (mg/dL)	93±13.8	97±17.3	0.11
Creatinine (mg/dL)	0.71±0.19	0.76±0.13	0.13
Na (mEq/L)	139±2.9	140±2.2	0.10
K (mEq/L)	4.3±0.4	4.4±0.3	0.25
Ca (mg/dL)	9.1±0.4	9.0±0.4	0.11
AST (mg/dL)	22 (7-87)	19 (12-39)	0.27
ALT (mg/dL)	21 (5-77)	20 (6-52)	0.85
LDL (mg/dL)	103±34.9	111±29.6	0.20
HDL (mg/dL)	47±14.2	42±8.8	0.01
hs-CRP (mg/dL)	2.86±3.78	0.39±0.18	<0.001
Wight blood cell, x109/L	8.8±2.7	7.8±1.9	0.01
Hemoglobin (mg/dL)	11.9±1.7	13.6±1.3	<0.001

Na: Sodium; K: Potassium; Ca: Calcium; AST: Aspartate aminotransferase; AST: Alanine transaminase; LDL: Low density lipoprotein; HDL: High density lipoprotein; CRP: C-reactive protein

All patients were examined to be in sinus rhythm and were asymptomatic in terms of cardiac symptoms. Patients and control subjects with diabetes mellitus, hypertension, valvular heart disease, coronary artery disease, wall motion abnormalities, left ventricular ejection fraction below 50%, severe pulmonary disease, malignancy, kidney/hepatic failure, incomplete/complete bundle branch block, atrial fibrillation, and paced rhythm were excluded from the analysis. Patient's clinical and demographic data were collected from the outpatient and inpatient files and from the electronic database of the hospital.

Information including gender, age, smoking status, and hyperlipidemia were gathered. The status of hyperlipidemia was based on the presence of a blood cholesterol level of ≥200 mg/dL or a triglyceride level of ≥150 mg/dL in the fasting state. Smoking was defined as current smoking or ex-smokers who forwent smoking in the past 6 months.

Electrocardiography

The 12-lead ECG was recorded at a paper speed of 50 mm/s (Nihon Kohden, Tokyo, Japan) at rest in the supine position. Resting heart rate was measured from the ECG taken during the patient evaluation. To decrease the error measurements, QT and QRS intervals were measured manually with calipers and magnifying glass. ECG measurements of QT and QRS intervals were performed by two cardiologists who were blinded to the patient data. The measurements were performed on lead II and lead V5 and then the longest QT interval was selected for analysis. The QT interval was measured from the beginning of the QRS complex to the end of the T wave, and the QT interval was corrected using the Bazett's formula: $QTc=QT\sqrt{}$ (R-R interval). Inter- and intraobserver coefficients of variation were found to be 2.3% and 2.6%, respectively.

Echocardiography

All echocardiographic examinations were performed by a certified cardiologist experienced in this field using a Vivid–7 (GE Vingmed, *Horten*, *Norway*) device in compliance with the American Society of Echocardiography (ASE) guidelines (12). Left ventricular ejection fraction was measured by using modified Simpson's rule on apical 4-chamber views

Laboratory

Laboratory findings were gathered from the hospital database. Following a 12-hour fasting period, blood samples for the complete blood count analysis were collected before the procedure in ethylenediamine tetra-acetic acidy anticoagulated Monovette tubes (Sarstedt, Leicester, United Kingdom). Total and differential leukocyte counts were measured by an automated hematology analyzer (Abbott Cell-Dyn, 3700; Abbott Laboratory, Abbott Park, Illinois, USA). Fasting blood glucose was determined using the hexokinase method. Plasma levels of triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were evaluated using an automated chemistry analyzer (Aeroset, Abbott, USA) with commercially available kits (Abbott, USA). Serum level of c-reactive protein(CRP) was measured by rate turbidimetry on the Beckman Coulter (California, USA).

Statistical analysis

Continuous variables were expressed as a mean±standard deviation or as median with interquartile range, and categorical variables were expressed as number and percentages. A c^2 test or Fisher's exact test was performed to compare the categorical variables. Correlations were assessed using the Spearman's rank test. Student's t-test or Mann–Whitney U test was used for continuous variables, as appropriate. The Pearson correlation test was used for correlation analysis. All statistical analyses were performed with SPSS (SPSS Inc., Chicago, IL, USA) software version 17.0 (SPSS Inc., Chicago, IL). A p value of 0.05 was considered statistically significant.

RESULTS

The study included 60 consecutive patients (37 females, 23 males; mean age, 49.4±11.7 y) who were diagnosed as having RA and the control group comprised 60 age- and gender-matched healthy volunteers (36 females, 24 males; mean age, 45.3±12.6 y) selected among healthy volunteers. Baseline clinical characteristics and laboratory parameters of the study groups are listed in Table 1. The baseline demographic and clinical characteristics of the study patients were similar (all p>0.05). The levels of high-density lipoprotein (HDL) cholesterol, white blood cell (WBC), and high-sensitivity CRP (hsCRP) levels were higher in the RA group (p<0.05). On the other hand, the RA group had lower hemoglobin levels than the control group (p<0.001)

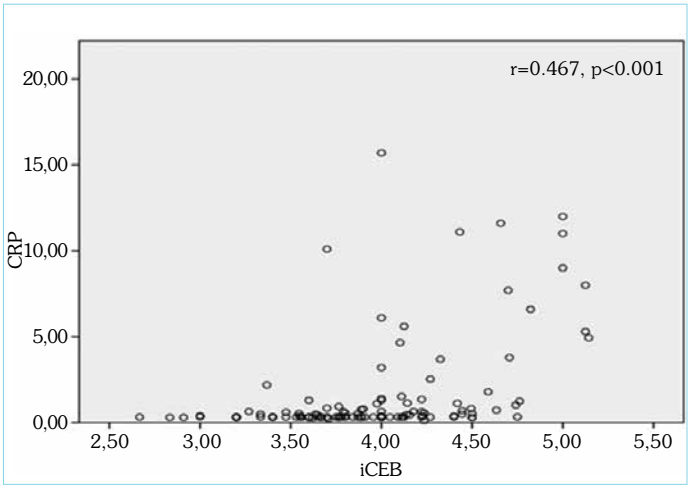

Figure 1. Correlation between hs-CRP levels and iCEB (QT/QRS)

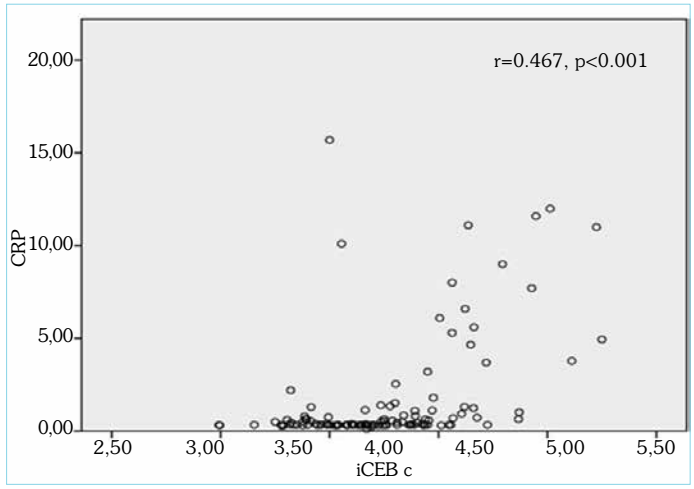

Figure 2. Correlation between hs-CRP levels and iCEBc (QTc/QRS)

Table 2. Echocardiographic and electrocardiographic characteristics of the study population

	Rheumatoid Arthritis Patients (n=60)	Control Subjects (n=60)	p
Ejection Fraction (%)	61±5.8	63±5.6	0.06
LVEDD (mm)	45±2.5	46±3.2	0.08
LVESD (mm)	29±3.8	29±3.8	0.45
Left atrial diameter (mm)	32±3.8	33±3.9	0.12
Heart rate (bpm)	80±13.1	76±13.6	0.07
QT interval (ms)	364±29.9	362±29.4	0.65
QTc interval (ms)	419±42.3	405±32.3	0.04
QRS interval (ms)	87.6±6.9	97.8±10.2	<0.001
Tp-e interval (ms)	77.6±7.3	74.1±7.3	0.01
Tp-e/QT ratio	0.21±0.02	0.20±0.02	0.04
iCEB (QT/QRS)	4.18±0.46	3.73±0.43	<0.001
iCEBc (QTcB/QRS)	4.82±0.69	4.17±0.50	<0.001

Data are represented as mean values±SD
LVEDD: Left Ventricle End Diastolic Diameter; LVESD: Left Ventricle End Systolic Diameter; mm: millimeters; bpm: beats per minute; Tp-e interval: T-peak to T-end interval; c=rate corrected value; B=corrected with Bazett's formula; iCEB=index of cardio-electrophysiological balance

Electrocardiography and echocardiographic findings are presented in Table 2. There were no difference between the two groups in terms of left ventricular ejection fraction (p=0.06) and left atrial diameter (p=0.12). Tp-e intervals, heart rate corrected QT (QTc) intervals, and Tp-e/QT ratios were higher; QRS duration was lower in patients with RA than in control subjects (all p<0.05). iCEB, defined as QT interval divided by QRS duration (p<0.001), and iCEBc, defined as QTc interval divided by QRS duration, were higher in patients with RA (p<0.001). In correlation analysis, iCEB and iCEBc levels were correlated with hsCRP levels (r=0.467, p<0.001 and r=0.479, p<0.001, respectively) (Figures 1 and 2).

DISCUSSION

In the current study, we observed that iCEB (QT/QRS) is higher in patients with RA than in healthy subjects. Additionally, iCEBc (QTc/QRS) is higher in patients with RA than in control subjects. To our best knowledge, this might be the first study demonstrating the link between iCEB and patients with RA. In the RA group, WBC and hsCRP levels were higher than the control group. RA is a systemic inflammatory autoimmune disease and these markers increase due to inflammation. Patients with RA had lower hemoglobin levels, which can be explained by anemia of chronic illness.

Recent studies revealed that patients with RA have an increased risk of mortality when compared to general population; it has also been reported that cardiovascular diseases are the greatest cause of death in patients with RA (2, 13). John et al. (3) demonstrated that SCD is two times higher in patients with RA than in healthy subjects. Sudden deaths may be explained with the increased incidence of malign arrhythmias.

Arrhythmogenic mechanism of RA is not well-known. Ischemic heart disease (IHD) and heart failure (HF) are frequently seen in patients with RA (14). It was demonstrated that IHD and HF are associated with malignant arrhythmias and SCD (15); as a result, these heart diseases may also lead to arrhythmic events in patients with RA. Myocardial fibrosis is a well-known complication of RA, which is thought to develop due to chronic inflammation (16). Consequently, fibrosis in the myocardium may cause arrhythmic events in RA.

Recent studies have suggested that QTc and QTd are related with malignant ventricular arrhythmias (17, 18). It has also been proposed that QTc and QTd are significantly increased and associated with mortality in patients with RA (5, 19, 20). In addition, inflammatory markers in blood circulation are correlated with QTc levels (21). Similarly, we also found a correlation between hsCRP levels and iCEB. Tp-e and Tp-e/QT ratio are new indexes that indicate ventricular repolarization defects. Prolongation of these markers are associated with malign arrhythmias (22-24). Acar et al. (8) observed that patients with RA have increased TP-e and TP-e/QT ratio when compared with healthy subjects. These indexes only cover alterations in ventricular repolarization.

Recently, in an animal study, a new non-invasive marker-iCEB between the depolarization and repolarization of the action potential-has been defined as a potential risk marker for drug-induced ventricular arrhythmias (9).

iCEB is calculated as QT interval divided by QRS interval on surface ECG. It was demonstrated by an electrophysiological study that iCEB is equal to the cardiac wavelength l (10). Cardiac wavelength l is taken as the conduction velocity (CV) multiplied by effective refractory period (ERP) (25). The relationship between cardiac wavelength l and malignant ventricular arrhythmias is well-known (26-28).

While sotalol administration increases iCEB and causes torsade de Pointes (TdP), flecainide usage decreases iCEB and causes non-TdP ventricular tachycardia or ventricular fibrillation (10). Indeed, it is true that iCEB reflects the balance between cardiac depolarization and repolarization, and both reduced and elevated iCEB are related with malignant arrhythmias.

In the present study, we observed that iCEB is higher in patients with RA than in healthy subjects. Higher iCEB is associated with TdP ventricular tachycardia. SCD in patients with RA may be related with TdP. iCEB, which is a simple and readily available index, can be used as a prognostic indicator to determine arrhythmic risk in RA. Therefore, our findings may be a reference for further studies.

Study Limitations

Our study has some limitations. The first one is that we considered a relatively small sample size. Second, it has a cross-sectional design and the patients were not followed-up. In addition, due to the diurnal variations in ECG parameters, 24-hour Holter ECG recording may be more valuable for evaluating dispersion of ventricular repolarization. We were unable to evaluate the relationship between ventricular arrhythmias and iCEB. The study population could not be followed up prospectively for ventricular arrhythmic episodes. Therefore, more comprehensive studies are still warranted to corroborate the predictive value of the iCEB in patients with RA.

CONCLUSION

We demonstrated that iCEB was increased in patients with RA. iCEB have advantages over the current indexes. Transmural dispersion of the T wave and instability of the QT interval only cover alterations in repolarization. But this non-invasive, simple, and new biomarker reflects the balance between the depolarization and repolarization of the cardiac action potential.

It is known that high iCEB is associated with TdP ventricular tachycardia. The increased frequency of SCD in patients with RA may be TdP-related. Further and large-scale prospective studies are required to clarify the prognostic importance of new index of balance between depolarization and repolarization (iCEB) in predicting arrhythmias in patients with RA.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Trakya University Medical Faculty Scientific Research.

Informed Consent: Informed consent is not necessary due to the restorsrective nature of the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Conceived and designed the experiments or case:FMU, MAY, GT. Performed the experiments or case: FMU, MAY. Analyzed the data: FMU, GT. Wrote the paper: FMU.

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

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