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Original Article

Investigating Novel Electrocardiographic Ventricular Repolarization Markers in Scleroderma Patients

Skleroderma Hastalarında Elektrokardiyografik Yeni Ventriküler Repolarizasyon Belirteçlerinin Araştırılması

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ABSTRACT

Objective: Ventricular repolarization involves the J-wave, ST-segment, T-wave, and U-wave on the surface electrocardiography (ECG). QT dispersion, Tp-e interval, Tp-e/QT, Tp-e/QTc, Tp-e/JT, and Tp-e/JTc ratios are some indices that predict ventricular tachyarrythmias. Although studies, evaluating repolarization abnormalities in scleroderma have frequently focused on Tp-e interval, QT, and Tp-e/QT, in our study, we aimed to investigate the risk of ventricular arrhythmia by using Tp-e/JT and Tp-e/JTc ratios, which are relatively new parameters.
Method: The study comprised 42 patients with scleroderma (mean age: 50.8 ± 7.3 years; 38 women and 4 men) and 40 healthy controls (mean age: 47.9 ± 5.5 years; 37 women and 3 men). We leveraged a standard 12-lead ECG recording to measure Tp-e interval, Tp-e/JT, Tp-e/JTc, Tpe/QTc, and Tp-e/QT parameters for each patient.
Results: Compared to the scleroderma patients electrocardiographic repolarization parameters including Tp-e (90.8 ± 10.9 vs 77.0 ± 10.2, p<0,001); QTc (423.7 ± 17.7 vs. 399.9 ± 25.9, p<0.001), Tp-e/QT (0.24 ± 0.02 vs. 0.21 ± 0.03, p<0.001); Tp-e/QTc (0.21 ± 0.02 vs. 0.19 ± 0.02, p<0.001); Tp-e/JT (0.31 ± 0.05 vs. 0.27 ± 0.05, p<0.001); Tp-e/JTc (0.27 ± 0.04 vs. 0.24 ± 0.03, p<0.001) were significantly lower in the control group.
Conclusion: The results suggest that ventricular arrhythmia predictors are significantly higher in patients with scleroderma compared to healthy individuals.

Keywords: Scleroderma, Tp-e/JT ratio, Tp-e/JTc ratio, Tp-e/QTc ratio, Tp-e/QT ratio

ÖZ

Amaç: Yüzey elektrokardiyografisinde (EKG), ventriküler repolarizasyon J dalgası, ST segmenti, T dalgası ve U dalgasını içerir. QT dispersiyonu, Tp-e aralığı, Tp-e/QT oranı, Tp-e/QTc oranı, Tp-e/JT, Tp-e/JTc oranları ventriküler taşiaritmileri öngören bazı göstergelerdir. Sklerodermada repolarizasyon anormalliklerini değerlendiren çalışmalar sıklıkla QT, Tp-e aralığı ve Tp-e/QT'ye odaklansa da, biz çalışmamızda nispeten yeni parametreler olan Tp-e/JT, Tp-e/JTc oranlarını kullanarak ventriküler aritmi riskini araştırmayı amaçladık.
Yöntem: Çalışma 42 sklerodermalı hasta (ortalama yaş; 50,8 ± 7,3, kadın 38 ve 4 erkek) ve 40 sağlıklı kontrolden (ortalama yaş; 47,9 ± 5,5, kadın 37 ve 3 erkek) oluştu. Her hasta için Tp-e aralığı ve Tp-e/JT, Tp-e/JTc, Tpe/QTc, Tp-e/QT oranları ölçmek için standart 12 derivasyonlu EKG kullandık.
Bulgular: Kontrol grubu ile karşılaştırıldığında, elektrokardiyografik repolarizasyon parametreleri olan Tp-e (90,8 ± 10,9'a karşılık 77,0 ± 10,2, p <0,001); QTc (423,7 ± 17,7'ye karşı 399,9 ± 25,9, p <0,001), Tp-e/QT (0,24 ± 0,02'ye karşılık 0,21 ± 0,03, p <0,001); Tp-e/QTc (0.21 ± 0.02'ye karşı 0,19 ± 0,02, p <0,001); Tp-e/JT (0,31 ± 0,05'e karşı 0,27 ± 0,05, p <0,001); Tp-e/JTc (0,27 ± 0,04'e karşı 0,24 ± 0,03, p <0,001) skleroderma hastalarında anlamlı olarak daha yüksek saptandı.
Sonuç: Sonuçlar, sağlıklı bireylere kıyasla sklerodermalı hastalarda ventriküler aritmi öngörücülerinin anlamlı olarak daha yüksek olduğunu göstermektedir.

Anahtar kelimeler: Skleroderma, Tp-e/JT oranı, Tp-e/JTc oranı, Tp-e/QTc oranı, Tp-e/QT oranı

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INTRODUCTION

Scleroderma is a systemic and chronic disease, characterized by progressive fibrosis in multiple organs (1). If the heart is involved in scleroderma, it is associated with a poor outcome (2). The myocardium, conduction system, pericardium, and coronary arteries can be involved (2). Cardiac involvement is most often asymptomatic; therefore its actual frequency is unknown. Cardiac manifestations in scleroderma may result in arrhythmias, conduction system abnormalities, direct myocardial disease, coronary artery disease, heart failure, pulmonary hypertension, pericardial disease, and rarely, primary valvular involvement (3). Myocardial fibrosis and pericardial disease are the most common diseases found in autopsy studies (4). Myocardial involvement, particularly ventricular arrhythmia, is the most common cause of death in patients with scleroderma after pulmonary fibrosis and pulmonary hypertension (5). Early identification of arrhythmias is important in patients with scleroderma due to their higher mortality rates.

Ventricular repolarization involves the J-wave, ST-segment, T-wave, and U-wave on the surface electrocardiography (ECG). Dispersion of ventricular repolarization has long been acknowledged as a predictor of ventricular arrhythmias (6).

QT dispersion, Tp-e interval, Tp-e/QT, Tp-e/QTc , Tp-e/JT, and Tp-e/JTc ratios are some indices that predict ventricular tachyarrythmias (7). Studies, evaluating repolarization abnormalities in scleroderma have frequently focused on QT, Tp-e interval, and Tp-e/QT.

The purpose of this study was to investigate relatively new ventricular repolarization parameters (Tp-e/JT, Tp-e/JTc ratios) in patients with scleroderma.

MATERIAL and METHODS

Study population

A total of 42 patients with scleroderma and 40 healthy individuals were enrolled in the study. 2013 American College of Rheumatology/European League Against Rheumatism criteria for scleroderma was used to classification of patients (8). Patients were followed up in both rheumatology and cardiology outpatient clinics. Basic demographic data including age, gender, BMI, blood pressure, comorbidity, and smoking of patients were recorded.

Pregnants, patients with known neoplasm, end-stage renal failure (eGFR <15 ml/min/1.73 m^2), liver failure, coronary artery, and structural heart disease, pulmonary hypertension, arrhythmias, and those receiving antiarrhythmic medications were excluded. Patients with ECG abnormalities such as bundle branch block or atrioventricular conduction abnormalities were also excluded. We excluded from the study patients with left bundle branch block (n:1), right bundle branch block (n:2), ST-segment depression on ECG (n:4), atrial fibrillation (n:1), history of mitral valve operation (n:1) and 5 patients who were taking beta-blockers or non-dihydropyridine calcium channel antagonists.

All patients underwent transthoracic echocardiography to rule out structural heart disease and pulmonary hypertension. Echocardiographic procedures were performed with the 4-Mhz transducer of Vivid S6 brand ultrasound (GE Vingmed, N-3191 Horten-Norway). All echocardiographic images were taken with the patients laid on their left side.

Electrocardiogram and measurement of indices

Standard 12 lead resting ECG tracing was taken with Nihon Kohen Cardiofax ECG-1950 VETat 25 mm/s paper speed and 10 mm/mV amplitude.

A magnifying Glass (TorQ 150 mm Digital Caliper LCD) was used for ECGs' measurements. QRS, QTc, QTd, Tp-e, JTc, JTd, and Pd were measured.

The QT interval is the distance between the onset of the QRS complex and the end of the T wave. Correction of the QT for the variations in heart rates was made with Hodges's formula [QTc= QT+0.00175x(HR-60)].

The QT dispersion (QTd) was determined as the

difference between the maximum and minimum QT intervals. Correction of the QTd for the variations in heart rates was made with Hodges's formula [QTd= QT+0.00175x(HR-60)]

The Tp-e interval, located between the peak and end of the T wave on ECG, was measured from the precordial leads. When U wave was present, the end of the T wave was defined as the lowest point of the curve between the T and U waves. The Tp-e/QT and Tp-e/QTc ratios were calculated by dividing Tp-e by either QT or QTc, respectively.

The JT intervals were measured from the end of the QRS complex (J point) up to the end of the T wave (JT end interval).

The JTc value was calculated by using Hodges' formula [JTc = JT+0.00175x(HR-60)].

The JTd was defined as the difference between the longest and shortest JT intervals.

Most commonly Bazett formula was used for the correction of QT. However, the Bazett formula overcorrects with heart rates >110 bpm and undercorrects with heart rates < 60 bpm (9). The Hodges correction and the Framingham correction do not contain similar problems and therefore we used Hodges's formula. Also, we were mostly experienced with Hodges' formula.

All measurements were calculated by two blinded cardiologists, and the average of 3 ECG values was used for the calculation. The intra- and inter-observer variations in measurement were less than 5%.

The study was approved by the institutional review board (2019/274).

Statistical Analysis

Analyses were carried out using SPSS 16.0 Statistical Package Program for Windows (SPSS Inc, Chicago, Illinois, USA). Quantitative variables were expressed as mean±standard deviation (SD), and qualitative variables as numbers and percentages. Differences between independent groups were assessed by Student t-test for normally distributed quantitative variables and Mann-Whitney U-test for variables without normal distribution and chi-square test for qualitative variables. All results were considered statistically significant at the level of $p \leq 0.05$.

RESULTS

Baseline patient demographics, including age, sex, and clinical risk factors were compared between the groups (Table 1). Demographic data were similar between the two groups except for age (50.8±7.3 vs. 47.9±5.5, p=0.045), presence of hypertension [14(33.3%) vs. 3(7.5%), p<0.001), and smoking (1 (2.4%) vs. 5(12.5%), p =0.013].

The patients with scleroderma had significantly higher values for the following parameters: Tp-e (90.8±10.9 vs 77.0±10.2, p<0,001); QTc (423.7±17.7 vs. 399.9±25.9, p<0.001), Tp-e/QT (0.24±0.02 vs. 0.21±0.03, p<0.001); Tp-e/QTc

Table1.Baseline parameters of the study groups

Baseline characteristics	Scleroderma (n=42)	Control group (n=40)	P value
Age (mean±SD) (years)	50.8±7.3	47.9±5.5	0.045
Male/female	4/38	3/37	0.747
Hypertension (%)	14(33.3%)	3(7.5%)	<0.001
Smoking	1(2.4%)	5(12.5%)	0.013
Diabetes mellitus	2(4.8%)	0(0%)	0.166
BMI	27.7±4.7	26.4±4.7	0.232

BMI, Body mass index; SD, standard deviation

Table 2. Electrocardiographic findings of the study population

	Scleroderma (n=42)	Control group (n=40)	P value
Heart rate (bpm)	77.9 ±12.3	74.6 ±15.6	0.284
QTmin ms	363.3±22.3	353.7 ±28.0	0.088
QTmax ms	385.1±23.4	373.0±25.9	0.029
QTc ms	423.7±17.7	399.9±25.9	<0.001
QTd ms	21.7±6.7	19.2±11.1	0.223
cQTd ms	24.4±7.2	21.6±12.2	0.210
Tp-e ms	90.8±10.9	77.0±10.2	<0.001
JTc ms	327.1±25.4	318.3±26.3	0.128
Tp-e/QT	0.24±0.02	0.21±0.03	<0.001
Tp-e/QTc	0.21±0.02	0.19±0.02	<0.001
Tp-e/JT	0.31±0.05	0.27±0.05	<0.001
Tp-e/JTc	0.27±0.04	0.24±0.03	<0.001
QRS ms	85.1±9.6	86.7±11.2	0.493

bpm, beat per minute; ms, millisecond; Tp-e, T peak and end interval; QTmin, minimum QT; QTmax, maximum QT; QTc, Corrected QT interval; JT interval (JT), were measured from the end of the QRS complex (J point) to the end of the T wave (JTend interval); JTc, Corrected JT interval; QTd, QT dispersion; cQTd, Corrected QT dispersion.

(0.21±0.02 vs. 0.19±0.02, p<0.001); Tp-e/JT (0.31±0.05 vs. 0.27±0.05, p<0.001), and Tp-e/JTc (0.27±0.04 vs. 0.24±0.03, p<0.001) (Table 2).

DISCUSSION

In this study, we found that scleroderma patients had higher values for Tp-e interval, Tp-e/JT, Tp-e/JTc, Tp-e/QTc and Tp-e/QT ratios on the surface ECG as compared with the healthy group. Tp-e/JT and Tp-e/JTc ratios are relatively new parameters, which have been known to be independent risk factors for malignant ventricular arrhythmias and sudden cardiac death, and they have been also used in various diseases in the literature (10, 11). To the best of our knowledge, up to now these markers have not been used in patients with scleroderma.

Based on the large database of the European League Against Rheumatism (EULAR) Scleroderma Trials and Research (EUSTAR), arrhythmias account for 6% of all-cause mortality in scleroderma (5). Underlying mechanisms of cardiac involvement in scleroderma are microvascular alterations, overproduction of extracellular matrix deposition by altered fibroblast, and dysregulation of the complex immune system (12). Patchy myocardial fibrosis seen in histological examinations may also affect the conduction system (13).

Potentially malign ventricular arrhythmias may be the first clinical presentation of sudden death. Also, the severity and presence of these arrhythmias are not correlated with clinical symptoms or signs of the disease; therefore these hidden markers of ECG can alert the clinicians. ECG is simple, cheap, and widely used modality for this purpose.

Dispersion of ventricular repolarization has been known as a substrate for ventricular arrhythmias (6). QT dispersion, Tp-e interval, and Tp-e/QT ratio are some parameters that evaluate ventricular repolarization (14, 15).

Scleroderma is associated with prolonged Tp-e interval and higher Tp-e/QT ratio (6). Tp-e interval is a measurable transmural dispersion of

repolarization in the left ventricle. Prolongation of this interval represents a period of potential vulnerability to re-entrant ventricular arrhythmias and sudden death even in patients with normal or un-measurable QTc (16). While QT dispersion and Tp-e interval may be affected by BMI and heart rate, the Tp-e/QT ratio is more specific (7).

In this present study, we have also found higher Tp-e/JT and Tp-e/JTc ratios in scleroderma. JT interval is a more specific repolarization marker, in that the QT range represents depolarization and repolarization, and is affected by QRS time interval (17). Furthermore, the Tp-e/JTp ratio can be regarded as a more sensitive index for recognition of arrhythmias as compared with the Tp-e or QT interval used individually.

Therefore, early diagnosis of malignant ventricular arrhythmias using these new markers may be of crucial help in predicting the prognosis of scleroderma patients. Although further studies are warranted before recommending routine measurements of Tp-e interval and Tp-e/JT, Tp-e/JTc, Tp-e/QTc, Tp-e/QT in all scleroderma patients.

Limitation of the study is that it is single-centered research conducted on a relatively small number of patients. The lack of follow-up of the patients is another limitation. Larger scale, prospective, and multicenter studies with longer follow-up are needed to determine the predictive value of the ECG.

CONCLUSION

Arrhythmias are important and frequent manifestations in scleroderma patients. Since their higher mortality risk, the early diagnosis of malignant arrhythmias is very important. ECG is a simple, cheap, and generally used test. Ventricular repolarization markers measured on ECG can alert clinicians in the early diagnosis of life-threatening arrhythmias. Cardiac involvement is much more frequent than expected based on clinical symptoms, therefore heart checkup tests and resting ECG monitoring should be included in the routine workup of scleroderma patients.

Disclosure Statement
The authors have no conflicts of interest to declare.

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