

USEFULNESS OF ELECTROCARDIOGRAPHIC MARKERS TO PREDICT VENTRICULAR ARRHYTHMIAS IN ACUTE MYOCARDITIS PATIENTS

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ABSTRACT

Aims: Acute myocarditis is an inflammatory disease of the myocardium and is characterized by a large heterogeneity of clinical presentation. Myocarditis is becoming to be recognized as a contributor to unexplained mortality, and is thought to be a major cause of sudden cardiac death in the first two decades of life. Myocardial inflammation, ion channel dysfunction, electrophysiological and structural remodelling may play important roles in life-threatening arrhythmias. We aimed to investigate the ventricular arrhythmia predictors in myocarditis patients by using electrocardiographic markers.

Methods: A total of 56 patients (mean age 22.5 ± 3.7 years; 89% males) with acute myocarditis were enrolled in the study. Tpeak-Tend intervals, Tpeak-Tend/QT and Tpeak-Tend/corrected QT (QTc), cardio-electrophysiological balance (QT/QRS) and heart rate-corrected QT(QTc)/QRS ratios were calculated from 12-lead electrocardiogram.

Results: Heart rate, QT and QTc values were similar between groups. QRS complexes were lower in arrhythmia positive group than arrhythmia negative group ($p=0.004$). Tpeak-Tend intervals, Tpeak-Tend/QT, Tpeak-Tend/QTc, cardio-electrophysiological balance and heart rate-corrected QT(QTc)/QRS values were significantly higher in arrhythmia positive group (< 0.001 , < 0.001 , $p=0.03$, $p=0.04$ and < 0.001 , respectively).

Conclusion: In this study, we observed that higher Tpeak-Tend, Tpeak-Tend/QT, Tpeak-Tend/QTc, cardio-electrophysiological balance (ICEB) and heart rate-corrected QT(QTc)/QRS ratio are associated with ventricular arrhythmic episodes in acute myocarditis patients. These electrocardiographic markers may be beneficial to identify high risk patients for arrhythmias complicating myocarditis.

Keywords: Arrhythmia, electrocardiography, myocarditis

INTRODUCTION

Acute myocarditis (AM) is an inflammatory disease of the myocardium and characterized by a large heterogeneity of clinical presentation (1). Viral myocarditis is thought to be a major cause of unexplained sudden cardiac death due to ventricular dysfunction, heart block and arrhythmia. According to a study, viruses can modify activity of ion channels or stimulate structural remodelling of the myocardium (2). On the other hand, ion channel dysfunction may be due to reasons.

The diagnosis of myocarditis traditionally relies on an invasive method, endomyocardial biopsy (3). Blood tests, echocardiography, Polymerase Chain Reaction

(PCR) and Magnetic Resonance Imaging (MRI) are also beneficial for the diagnosis of myocarditis. Although electrocardiography is a nonspecific examination for diagnosis, it can present atrioventricular blocks, atrial and ventricular arrhythmias and ST segment elevation in myocarditis patients.

Recently, more specific electrocardiographic indexes and markers for arrhythmic events came into use (4-7). As these indexes; fragmented QRS, cardio-electrophysiological balance (ICEB) which is calculated by the division of QT interval to time of QRS and the Tpe/QT ratio $[(Tpeak-Tend)/(QT)]$ are simple markers and can be easily measured and their relationships with arrhythmic events were demonstrated.

This is the first study on electrocardiographic markers role to predict arrhythmias in patients with myocarditis. In this study, we planned to investigate the ventricular arrhythmia predictors in myocarditis patients by using electrocardiographic markers.

MATERIAL AND METHODS

This study was approved by Scientific Researches Ethics Committee of Trakya University Medical Faculty. In this study, the data of 56 patients treated with myocarditis or perimyocarditis in Cardiology Department of Trakya University Hospital from January 2010 to November 2016 were analyzed retrospectively. Firstly, the data of all patients who had myocarditis was retrieved and 56 patients who had chest pain were included in the study. The age range of population was between 0 and 30. The reports of epicrisis, lab-results, anamnesis of the patients and the reports of echocardiography were analyzed by using the electronic database of the hospital. And the electrocardiography reports in patients' folders stored in hospital archives were examined. The data was retrieved by using the protocol numbers of the patients.

As appeal to hospital and demographic data; age, gender, history of smoking and drinking alcohol, the presence of diabetes mellitus and hypertension, family history of myocardial infarction, systolic and diastolic blood pressure, ejection fraction, the results of echocardiograms, electrocardiograms and arrhythmias were included to analysis.

As results of laboratory; glucose, creatinine, sodium (Na), potassium (K), total cholesterol, triglyceride, high density lipoprotein (HDL), low density lipoprotein (LDL), aspartate aminotransferase (AST), alanine transaminase (ALT), hemoglobin, white blood cell (WBC), troponin I, C-reactive protein (CRP) and sedimentation values were included in the analysis.

As results of electrocardiography; heart rates, QT interval, QRS interval, T wave, Tpeak-Tend interval were recorded as data. Non-sustained ventricular tachycardia, sustained ventricular tachycardia and ventricular fibrillation were defined as ventricular arrhythmia.

As medical treatments; angiotensin receptor blockers (ARB) and the angiotensin converting enzyme inhibitors (ACE inhibitors), beta blockers, calcium blockers, non-steroidal anti-inflammatory drugs (NSAID), acetylsalicylic acid (ASA), colchicine were included in

the analysis.

Continuous variables are expressed as a mean \pm standard deviation or as median with interquartile range and categorical variables are expressed as numbers and percentages. Chi-square test or Fisher's exact test was performed to compare the categorical variables. Data was tested for normal distribution using the Kolmogorov-Smirnov test, Student's t-test or Mann-Whitney U test was used for continuous variables, when appropriate. Pearson's correlation test was used for correlational analysis. All statistical analyses were performed using SPSS software version 17.0 (SPSS Inc., Chicago, IL). A p-value of <0.05 was considered statistically significant.

RESULTS

The study population was composed of 56 patients who were diagnosed with myocarditis and perimyocarditis from January 2010 to November 2016. Baseline demographic, clinical characteristics and laboratory parameters of study subjects are summarized in Table 1.

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

	Arrhythmia (+) Patients (n=13)	Arrhythmia (-) Patients (n=43)	P Value
	92 % (12)	88 % (38)	0.68
Female % (n)			
Age	24 \pm 3.5	26 \pm 3.6	0.06
Hyperlipidemia % (n)	38% (5)	30% (13)	0.57
Smoking % (n)	23% (3)	11% (5)	0.30
Body Mass Index	26.6 \pm 3.7	26.5 \pm 3.2	0.39
Systolic Blood Pressure (mmHg)	108 \pm 14	113 \pm 13	0.31
Diastolic Blood Pressure (mmHg)	70 \pm 9	73 \pm 9	0.54
Glucose (mg/dL)	100 \pm 12.1	99 \pm 19.5	0.15
Creatinine (mg/dL)	0.87 \pm 0.19	0,81 \pm 0.10	0.20
Na (mEq/L)	138 \pm 2.3	139 \pm 2.5	0.64
K (mEq/L)	4.4 \pm 0.6	4.5 \pm 0.8	0.52
Ca (mg/dL)	9.3 \pm 0.3	9.2 \pm 0.4	0.24
AST (mg/dL)	63 (18-103)	51 (9-159)	0.59
ALT (mg/dL)	27 (12-50)	28 (9-70)	0.15
LDL (mg/dL)	94 \pm 31.8	97 \pm 29.9	0.41
HDL (mg/dL)	38 \pm 9.3	35 \pm 8.5	0.28
hs-CRP (mg/dL)	2.86 \pm 3.78	0,39 \pm 0.18	0.36
Troponin I (μ g/L)	4.13 \pm 3.71	4,03 \pm 4.36	0.14
Wight blood cell, x109/L	10.1 \pm 2.2	9.4 \pm 2.6	0.37
Hemoglobin (mg/dL)	15.3 \pm 1.2	14.3 \pm 1.4	0.67

Na: Sodium; K: Potassium; Ca: Calcium; AST: Aspartateaminotransferase; ALT: Alaninetransaminase; LDL: Low density lipoprotein; HDL: High density lipoprotein; CRP: C-reactive protein

Echocardiographic and electrocardiographic characteristics of the study population are shown in Table 2. Heart rate, QT and QTc values were similar between groups. QRS intervals were shorter in arrhythmia positive group than arrhythmia negative group ($p=0.004$). Tp-e intervals, Tp-e/QT, Tp-e/QTc, iCEB and iCEBc values were significantly higher in arrhythmia positive group ($p < 0.001$, $p < 0.001$, $p=0.03$, $p=0.04$ and $p < 0.001$, respectively)

Table 2: Echocardiographic and electrocardiographic characteristics of the study population

	Arrhythmia (+) Patients (n=13)	Arrhythmia (-) Patients (n=43)	P value
Ejection Fraction (%)	58 ±6.9	62 ±7.9	0.38
LVEDD (mm)	46 ±3.3	45 ±5.2	0.19
LVESD (mm)	31 ±2.1	230 ±4.5	0.79
Left atrial diameter (mm)	29 ±3.7	31 ±4.5	0.53
Heart rate (bpm)	98 ±25.6	88 ±16.6	0.09
QT interval (ms)	349 ±42.1	376 ±49.7	0.08
QTc interval (ms)	450 ±58.9	433 ±54.6	0.34
QRS interval (ms)	103 ±19.3	122 ±21.0	0.004
Tp-e interval (ms)	91 ±9.4	74 ±16.8	< 0.001
Tp-e/QT ratio	0,26 ±0,03	0,20 ±0,05	< 0.001
Tp-e/QTc ratio	0,20 ±0,03	0,17 ±0,04	0.03
iCEB (QT/QRS)	3,49 ±0,77	3,13 ±0,49	0.04
iCEBc (QTcB/QRS)	4,47 ±0,86	3,61 ±0,64	< 0.001

Data are represented as mean values ± Standart Deviation (SD). LVEDD: Left Ventricle End Diastolic Diameter ; LVESD : Left Ventricle End Systolic Diameter; mm: millimeters; bpm: beats per minute; ms: millisecond; 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

DISCUSSION

In this study, we observed that Tpe, Tp-e/QT, Tp-e/QTc, iCEB and iCEBc (QTc/QRS) were significantly higher in myocarditis patients who had ventricular arrhythmia. Furthermore, QRS interval was significantly shorter in patients with ventricular arrhythmia. To the best of our knowledge, this might reportedly be the first study demonstrating a link between new ECG markers and ventricular arrhythmia in myocarditis patients.

Myocarditis is mostly asymptomatic, therefore it is difficult to determine the frequency. In routine biopsy, myocarditis has been identified between 1-9%. In the studies, the incidence of myocarditis is found to be

between 1-80%. Infectious, toxic, pharmacologic and physical agents can cause acute myocarditis. In addition to these, autoimmune diseases can also be the cause. The most common bacterial causes of reduction have been the cause of viruses with myocarditis. Among viruses, enterovirus is the most common cause.

Sinus tachycardia was found to be the most frequent manifestation in ECG. Left bundle branch block was observed in 20% of myocarditis patients. Most frequently observed situation is sinus tachycardia and non-specific ST-T changes. In patients with congestive heart failure, left ventricular systolic dysfunction is common in echocardiography (8). Underlying etiology determines the prognosis of myocarditis (9). Recent studies have suggested that heart rate-corrected QT interval (QTc) and QT interval dispersion (QTd) are related with malignant ventricular arrhythmias (10, 11). In recent studies, the Tp-e interval, the interval between the peak and the end of the T wave, has been specified as an index of total dispersion of repolarization (12). Prolonged Tp-e interval may predict ventricular arrhythmias and mortality (13). Thus, Tp-e/QT ratio has been proposed to be a better marker of ventricular repolarization (14). iCEB between the depolarization and repolarization of the action potential-has been defined as a potential risk marker for drug-induced ventricular arrhythmias in an animal study trial (7). The relationship between ventricular arrhythmias and iCEB was demonstrated in a previous study (15).

Ion channelopathies, oxidative stress, inflammation and altered intracellular signaling are main possible mechanisms for ventricular arrhythmia in myocarditis. Together, these act to alter intercellular coupling, produce interstitial oedema and fibrosis, which would lead to conduction abnormalities. Abnormal Ca²⁺ handling and K⁺ channel down regulation lead to abnormal repolarization. Clinical and instrumental characteristics of the patients were used for the arrhythmic risk prediction of myocarditis (1). Prolonged QT duration was observed in patients with fulminant myocarditis and it is well known that malignant arrhythmias are observed more often in fulminant myocarditis (16). On the other hand, other non invasive and simple measurable markers as Tpe, Tpe/QT ratio, Tpe/QTc ratio, iCEB and iCEBc for ventricular arrhythmia prediction were not studied before.

Study:

Our study had some limitations. Due to the diurnal variations in ECG parameters, 24-hour Holter ECG recording could have been more valuable for evaluating dispersion of ventricular repolarization. ECG findings were measured manually with calipers and magnifying glass; manual measurements of intervals with a magnifying glass are less accurate than the automatic ones. Therefore, a more comprehensive study is needed to corroborate the predictive value of these ECG markers in patients with myocarditis.

In the end of the study, we concluded that the higher Tp-e, Tp-e/QT, Tp-e/QTc, iCEB and iCEBc are associated with ventricular arrhythmic episodes in acute myocarditis patients. These electrocardiographic markers may be beneficial to identify high arrhythmic risk for patients in myocarditis.

Ethics Committee Approval: This study was approved by Scientific Researches Ethics Committee of Trakya University Medical Faculty.

Informed Consent: Written informed consent was obtained from the participants of this study.

Conflict of Interest: The authors declared no conflict of interest.

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