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Assessment of repolarization abnormalities in baseline electrocardiograms of patients with myocarditis

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Background/aim: Myocarditis in the acute phase usually presents with sinus tachycardia but many other arrhythmias might be seen as well. In this study we aimed to investigate repolarization abnormalities in baseline ECG of patients with myocarditis for the first time.

Materials and methods: Thirty patients diagnosed with myocarditis and 25 healthy age-matched controls were included. Two different cardiologists measured corrected QT (QTc), QT dispersion (QTd), QT peak (QTp), T wave peak to T wave end (TpTe), TpTe/QT ratio, and TpTe/QTc ratio in 12-lead ECG.

Results: When compared with the control group, QTp (P: 0.021), QT (P: 0.003), TpTe (P < 0.001), TpTe/QTc ratio (P < 0.001), and TpTe/QT ratio (P: 0.005) were significantly higher in patients with myocarditis. A comparison of receiver operating characteristic (ROC) curves was conducted using the Hanley and McNeil method. The area under the curve (AUC) of the electrocardiographic characteristics QT (AUC: 0.736; 95% CI [0.600–0.846]), QTP (AUC: 0.680; 95% CI [0.540–0.799]), and TpTe (AUC: 0.771; 95% CI [0.638–873]) and TpTe/QTc (AUC: 0.774; 95% CI [0.641–0.876]) and TpTe/QT (AUC: 0.726; 95% CI [0.589–0.838]) in myocarditis were not significantly different from each other but all of them were different from 0.5.

Conclusion: Baseline ECGs of patients with myocarditis were associated with repolarization abnormalities. These novel findings may be one of the reasons underlying arrhythmic events in patients with myocarditis.

Key words: Myocarditis, repolarization abnormalities, TpTe

1. Introduction

Myocarditis is an inflammatory disease of the heart muscle produced by infectious or noninfectious causes (1). Viral infections are the most common presumed causes but incidence of myocarditis is highly variable in the published data. Diversity in etiology, clinical manifestations, and diagnostic criteria challenge physicians for determination of an algorithm. The clinical presentation of myocarditis can range from subclinical disease to life-threatening heart failure, cardiogenic shock, arrhythmia, or sudden cardiac death (2–4).

While sinus tachycardia is the most common arrhythmia, many different forms including life-threatening arrhythmias such as ventricular tachycardia can be seen during the myocarditis course (5). Even though the exact mechanisms leading to sudden cardiac death during myocarditis remain to elucidated, various molecular and immunopathogenetic reasons have been proposed. Arrhythmogenic substrates secondary to viral-induced myocardial injury may both invoke formation of reentry circuits and trigger ventricular arrhythmia by acting as a proarrhythmic substrate or causing ion channel dysfunction (5).

Recent studies showed that electrocardiographic indicators of myocardial repolarization, which are QT interval corrected QT (QTc) interval and QT dispersion (QTd), are associated with several conditions (6,7). Novel indices such as TpTe interval and TpTe/QT have emerged as markers associated with ventricular arrhythmias (6,7).

The present study aimed to investigate myocardial repolarization in patients with myocarditis and life-threatening ventricular arrhythmias by using the parameters QT, QTc, QTd, QT peak (QTp), TpTe/QT, and TpTe/QTc.

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2. Materials and methods

2.1. Study population

Our patient population consisted of 30 patients diagnosed with myocarditis between 2013 and 2015 in a retrospective fashion. Twenty-five healthy subjects with similar age and demographic characteristics who were admitted to the outpatient clinic for atypical symptoms were assigned as the control group. All of the patients had a recent history of upper or lower respiratory tract infection 2–3 weeks before the index event and no etiologic agents were identified except for in 2 patients in which influenza virus antigen was detected in nasal secretions. Medical history and physical examination, ECG, echocardiography, coronary angiography and cardiac biomarkers were used for diagnosis of myocarditis. Cardiac magnetic resonance (CMR) scanning was performed only in 2 patients.

Patients were excluded if they had coronary artery disease, moderate/severe valve disease, chronic lung diseases, severe hepatic and renal dysfunction, thyroid dysfunction, anemia, electrolyte imbalance, bundle branch block, atrioventricular conduction abnormalities on ECG and ECG without clearly analyzable QT-segment, or were receiving medications with effects on heart rhythm and conduction system (antiarrhythmic drugs, digitalis, β-blocker, calcium-channel blocker, antipsychotics, and antihistaminics).

2.2. Diagnosis of myocarditis

The diagnosis of myocarditis was made according to the criteria mentioned in the position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases, which were as listed below (1).

2.3. Clinical presentations

- Acute chest pain, pericarditic, or pseudoischemic
- New-onset (days up to 3 months) or worsening of: dyspnea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs
- Subacute/chronic (>3 months) or worsening of: dyspnea at rest or exercise, and/or fatigue, with or without left and/or right heart failure signs.
- Palpitation, and/or unexplained arrhythmia symptoms and/or syncope, and/or aborted sudden cardiac death
- Unexplained cardiogenic shock.

2.4. Diagnostic criteria

I. ECG/Holter/stress test features: Newly abnormal 12 lead ECG and/or Holter and/or stress testing, any of the following: I to III degree atrioventricular block, or bundle branch block, ST/T wave change (ST elevation or non-ST elevation, T wave inversion), sinus arrest, ventricular tachycardia or fibrillation and asystole, atrial fibrillation, reduced R wave height, intraventricular conduction delay (widened QRS complex), abnormal Q waves, low voltage, frequent premature beats, supraventricular tachycardia,

II. Myocardiocytolysis markers Elevated TnT/TnI,

III. Functional and structural abnormalities on cardiac imaging (echo/angio/CMR) New, otherwise unexplained LV and/or RV structure and function abnormality (including incidental finding in apparently asymptomatic subjects): regional wall motion or global systolic or diastolic function abnormality, with or without ventricular dilatation, with or without increased wall thickness, with or without pericardial effusion, with or without endocavitary thrombi,

IV. Tissue characterization by CMR edema and/or LGE of classical myocarditic pattern. Clinically suspected myocarditis if ≥1 clinical presentation and ≥1 diagnostic criteria from different categories, in the absence of: (1) angiographically detectable coronary artery disease (coronary stenosis ≥50%); (2) known preexisting cardiovascular disease or extracardiac causes that could explain the syndrome (e.g., valve disease, congenital heart disease, hyperthyroidism). If the patient is asymptomatic ≥2 diagnostic criteria should be met.

2.5. Echocardiography

All echocardiographic measures were performed according to the American Society of Echocardiography guidelines (8). Left ventricle (LV) dimensions were measured in the parasternal long axis view. From the parasternal axis, the aorta, left atrium, LV systolic and diastolic diameters, interventricular septum, and posterior wall thicknesses were measured as the patients were positioned in the left lateral decubitus position. Left ventricular ejection fraction (EF) was calculated by the Teichholz method.

2.6. Electrocardiography

Baseline 12-lead ECGs of patients with myocarditis were recorded with a paper speed of 25 mm/s and standardization of 1.0 mV/cm on the day of admission. R-R interval, QT interval, QTp, and TpTe intervals were manually measured by two experienced cardiologists blind to the clinical characteristics of the patients. QT interval was defined as the interval between from the beginning of the QRS complex to the end of T-wave. The QT intervals were corrected according to the formula of Bazzett, where $QTc = QT/\sqrt{RR}$. QT dispersion was calculated as the difference between longest and shortest QT intervals. TpTe interval was defined as the interval from the peak of the T wave to the end of the T wave. TpTe/QTc and TpTe/QT ratios were calculated from obtained measurements. Measurements were recorded from precordial leads.

2.7. Statistical analysis

Continuous variables are expressed as median [range]. Categorical data are shown in frequencies and percentages. The Mann–Whitney U test was used to compare differences between the groups due to the small sample size. Fisher's

exact test and continuity correction (Yate's correction) test were used to test the categorical variables. Receiver operating characteristics (ROC) curves were used to evaluate the effectiveness of each ECG parameter as a screening method for myocarditis. Comparison of ROC curves was performed to test the statistical significance of the difference among the area under the curve (AUC) dependent ROC curves (derived from the same cases) with the method of Hanley and McNeil. Statistical tests were 2-tailed, and results were regarded as significant at or below the 5% probability level. The intraclass correlation coefficient (ICC) and its 95% confidence interval (CI) were used to assess interobserver reliability between the first and the second cardiologist. Statistical Package for the Social Sciences (SPSS version 22.0, SPSS Inc., Chicago, IL, USA) and MedCalc software were used.

3. Results

The comparison of demographic characteristics is shown in the Table. Age, hypertension, diabetes mellitus, and smoking were matched between the patient and control groups. EF (61 [67–30] vs. 66 [74–54], P < 0.001), end systolic diameter (ESD) (3.1 [4.6–2.2] vs. 2.9 [3.7–2.3], P: 0.031), and E/a ratio (1.09 [1.8–0.5] vs. 0.7 [1.5–0.44], P: 0.032) were significantly different between the two groups as echocardiographic parameters. When compared with the control group, QTp (0.29 [0.34–0.25] vs. 0.27 [0.31–0.25], P: 0.021), QT interval (0.36 [0.43–0.32] vs. 0.34

Table. Basic clinical and laboratory characteristics of the patient and control groups.

	Patient (n: 30)	Control (n: 25)	P
Age, years	29 [52–20]	29 [38–22]	0.886
HT (%)	7 (30.4)	3 (14.3)	0.287
DM (%)	5 (20)	2 (10.5)	0.680
Smoking (%)	7 (23.3)	6 (24)	1
ECG characteristics			
QTp	0.29 [0.34–0.25]	0.27 [0.31–0.25]	0.021
QT interval, s	0.36 [0.43–0.32]	0.34 [0.40–0.30]	0.003
QTd interval, s	0.03 [0.08–0.01]	0.02 [0.05–0.01]	0.219
QTc interval, s	0.40 [0.46–0.36]	0.39 [0.43–0.33]	0.379
TpTe interval, s	0.10 [0.15–0.08]	0.09 [0.12–0.07]	<0.001
TpTe/QTc ratio	0.26 [0.33–0.20]	0.22 [0.29–0.17]	0.001
TpTe/QT ratio	0.28 [0.36–0.22]	0.25 [0.33–0.19]	0.005
Echocardiography			
LA size (cm)	3.4 [4.4–3]	3.4 [3.8–3]	0.858
EF (%)	61 [67–30]	66 [74–54]	<0.001
ESD (mm)	3.1 [4.6–2.2]	2.9 [3.7–2.3]	0.031
EDD (mm)	4.7 [6–2.8]	4.6 [6–4]	0.727
E wave, cm/s	0.68 [1.1–0.5]	0.60 [1.3–0.4]	0.135
A wave, cm/s	0.74 [1.3–0.4]	0.8 [1.2–0.4]	0.215
E/A ratio	1.09 [1.8–0.5]	0.7 [1.5–0.44]	0.032
E', m/s	0.10 [0.16–0.05]	0.08 [0.15–0.03]	0.073
E/E' ratio	7.5 [12–5]	8 [13–6]	0.308
Septum, cm	1.1 [1.2–0.8]	1.1 [1.3–0.8]	0.760
Posterior wall, cm	1.06 [1.2–0.6]	1.05 [1.3–0.8]	0.352
Basal troponin, ng/dL	0.30 [4–0]		

A wave: Late ventricular filling velocity, DM: Diabetes mellitus, E wave: Early ventricular filling velocity, EF: Ejection fraction, HT: Hypertension, LA: Left atrium, QTc: corrected QT, QTd: QT dispersion, QTp: QT peak, TpTe: T wave peak to T wave end

[0.40–0.30], P: 0.003), TpTe (0.10 [0.15–0.08] vs. 0.09 [0.12–0.07], P < 0.001), TpTe/QTc ratio (0.26 [0.33–0.20] vs. 0.22 [0.29–0.17], P < 0.001), and TpTe/QT ratio (0.28 [0.36–0.22] vs. 0.25 [0.33–0.19], P: 0.005) were significantly higher in patients with myocarditis. QT dispersion interval and QTc interval were not significantly different between the groups.

The area under the ROC curve (AUC) for the electrocardiographic characteristics QT (AUC: 0.736, 95% CI [0.600–0.846]), QTP (AUC: 0.680, 95% CI [0.540–0.799]), and TpTe (AUC: 0.771, 95% CI [0.638–0.873]) and TpTe/QTc (AUC: 0.774, 95% CI [0.641–0.876]) and TpTe/QT (AUC: 0.726, 95% CI [0.589–0.838]) in myocarditis were not significantly different from each other but all of them were different from 0.5 by the Hanley and McNeil method (Figure).

3.1. Reproducibility

QT interval, QTd, QTp, and TpTe interval were calculated by the first experienced cardiologist and then a second experienced cardiologist, who were blinded to the first measurements. The interobserver reproducibility of selected ECG parameters was satisfactory. For interobserver reliability ICCs were significant for QT interval (0.953; 95% CI [0.921–0.973]), QTp (0.956; 95% CI [0.925–0.974]), QTd (0.920; 95% CI [0.867–0.953]), and TpTe interval (0.881; 95% CI [0.804–0.929]).

4. Discussion

In the present study, we compared myocardial repolarization parameters in baseline ECGs of patients with myocarditis with those of the control group and found that QTp, QTc, TpTe interval, TpTe/QTc ratio, and TpTe/QT ratio were significantly higher in the patient group. When AUC values of these parameters were compared, none of them was superior for prediction of myocarditis.

Myocarditis can occur due to both infectious and noninfectious causes; however, the most common etiologic causes are viral agents. The most important causes of myocarditis in North America and Europe are enterovirus (especially Coxsackie virus), Parvo virus B19, and Human Herpes Virus 6 (HHV-6). Systemic diseases, cardiotoxic agents, agents that can induce hypersensitivity reactions, and many different types of bacteria, fungi, and parasites can cause myocarditis (9–11). Myocarditis may have a great variety of manifestations ranging from subclinical setting (fever, palpitation, exertional dyspnea, myalgia) to a fulminant course (hemodynamic collapse, syncope) (3,4). Because of variety in clinical presentations, it is hard to detect the real incidence of myocarditis precisely. Serious complications may occur in both the early and late phase of disease course; atrial and ventricular arrhythmias, total atrioventricular heart block with hemodynamic compromise, or sudden cardiac death may occur in the early course and heart failure in the late course (4,11,12). In the study by Felker et al., which recruited 1230 patients with unexplained heart failure, myocardial disease was considered to be the underlying reason in 9% of the patients (11). Furthermore, another study in which endomyocardial biopsy was performed in 2200 patients with unexplained

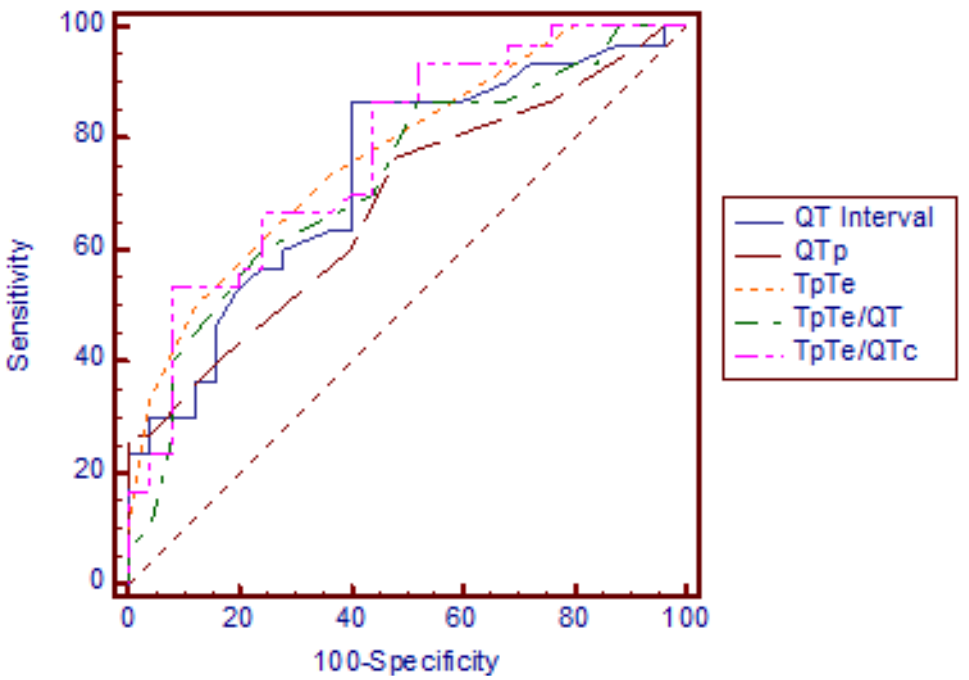

Figure. Comparison of ROC curves by the Hanley and McNeil method for myocarditis.

cardiomyopathy revealed that myocarditis was the underlying cause in 10% of the patients (13). In the context of sudden cardiac death, Drory et al. studied subjects aged <40 years suffering sudden unexpected death and showed that myocarditis was the underlying cause of sudden unexpected death in 22% of subjects aged less than 30 years while it was 11% in older patients (12). The medical history of our patient population suggests viral causes since no specific etiologic agent could be identified. Although impaired left ventricular systolic function was common in our patients, no life-threatening arrhythmia or sudden cardiac death was seen.

Previous studies demonstrated that fibrosis and scarring of myocardium, secondary hypertrophy, and atrophy can induce ventricular arrhythmias via ectopic pacemakers, late potentials, and reentry as a result of nonhomogeneous conduction. Meanwhile, ongoing inflammatory processes in the cardiac myocytes and interstitium may directly trigger arrhythmias through oscillations in membrane potential. Therefore, secondary changes due to ongoing inflammation in myocardial tissue may induce repolarization abnormalities associated with sudden cardiac death (14,15).

Ventricular myocardium contains 3 electrophysiologically distinct types of cells: epicardial, endocardial, and m-cell (myocardial) cells. M-cells have larger late-sodium and sodium/calcium exchange channels and weaker slowly activating delayed rectifier current and so they are more susceptible to repolarization-prolonging insult and serious ventricular arrhythmias (16). Myocardial repolarization is assessed by different indices including QT, QTc, QT dispersion, TpTe interval, TpTe/Qt ratio, and TpTe/QTc, which are accepted as indicators of QT dispersion, corrected QT dispersion, and transmural repolarization dispersion in various studies (7,17). Prolonged QTc was shown to be the most common ECG finding in a study that examined 20 patients with myocarditis and suffering serious complications (life-threatening arrhythmias) (18). Similarly, when Amoozgar et al. compared patients with Kawasaki disease and a control group, they took QT interval as an index of transmural dispersion of repolarization and found that both QT and QTc interval were prolonged in the patient group (19). Prolonged QT interval in hypertrophic cardiomyopathy was associated with nonsustained ventricular tachycardia in another study (20). Another well-investigated index of transmural dispersion of repolarization is TpTe, which was shown to be helpful for predicting the risk for life-threatening ventricular arrhythmias (21). Furthermore, previous studies reported that prolonged TpTe was associated with ventricular arrhythmia and sudden cardiac death in patients with hypertrophic cardiomyopathy (22), end-stage renal failure (23), inducible ventricular tachycardia (24), recent MI (25), long-QT syndrome (26), operated tetralogy of Fallot (27), and Brugada syndrome (28). TpTe/QT and TpTe/QTC, relatively novel markers for repolarization abnormalities, are not affected by heart rate and body mass in contrast to TpTe (29). Several conditions assumed to be associated with myocardial inflammation such as ankylosing spondylitis (30), rheumatoid arthritis (31), chronic hepatitis B (7), nondipper hypertension (32), and anabolic/androgenic steroid use (33) were also associated with prolonged TpTe and TpTe/QT.

In this study, we investigated ECG parameters associated with dispersion of repolarization in patients with myocarditis for the first time in the literature. Repolarization abnormalities are expected to occur due to pathologic processes of myocardial inflammation during the course of myocarditis. A simple way for recognition of repolarization abnormalities and estimation of the risk for life-threatening arrhythmias in myocarditis, which can have various clinical manifestations, may be helpful for optimal management of patients with myocarditis.

5. Conclusion

Baseline ECGs of patients with myocarditis were associated with repolarization abnormalities indicated by prolonged TpTe, TpTe/QTc, TpTe/QT, QTp, and QT interval measurements. This novel finding may be one of the reasons underlying arrhythmic events in patients with myocarditis.

6. Study limitations

The main limitations of our study were the retrospective design and small sample size. Utilization of cardiac MR imaging in all patients could have provided more detailed information about involved myocardial areas consistent with myocarditis.

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