Evaluation of ventricular arrhythmogenesis in children with acute rheumatic carditis

Mehmet Kucuk, Cem Karadeniz, Rahmi Ozdemir, Timur Meşe

Abstract

Background: Recent studies have shown that the Tp-e interval, which on an electrocardiogram (ECG) is the interval between the peak and the end of the T wave, can be used as an index of transmural dispersion of ventricular repolarisation (TDR). Both Tp-e/QT and Tp-e/QTc ratios have also been used in that capacity. However, these novel repolarisation indices have not previously been studied in children with acute rheumatic carditis (ARC).

Methods: A hundred and thirty-nine children who were diagnosed with ARC and 153 age- and gender-matched healthy controls were retrospectively reviewed. Twelve-lead ECGs were used to evaluate P-wave, QT and QTc dispersions, Tp-e interval, and Tp-e/QT and Tp-e/QT ratios.

Results: The mean age of the patients was 10.9 ± 2.4 years. The P-wave, QT and QTc dispersions were significantly higher in patients compared to the healthy control subjects. However, the novel repolarisation indices of Tp-e and Tp-e/QT have not been studied in RC patients previously. In this study, we aimed to assess the Tp-e interval and the Tp-e/QT ratio in children with ARC. Prolongation of the Tp-e interval and an increased Tp-e/QT ratio might be useful markers for predicting myocardial involvement in children with ARC.

Conclusions: This study showed that the new transmural dispersion of ventricular repolarisation parameters, Tp-e interval, Tp-e/QT ratios and QTd were increased in children with ARC. Prolongation of the Tp-e interval and an increased Tp-e/QT ratio might be useful markers for predicting myocardial involvement in children with ARC.

Keywords: acute rheumatic carditis, children, ventricular arrhythmogenesis, Tp-e interval, Tp-e/QT ratio, PWd, QTd

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Department of Paediatric Cardiology, Dr Behcet Uz Children’s Hospital, Izmir, Turkey
Mehmet Kucuk, MD, drmehmetkucuk@yahoo.com
Cem Karadeniz, MD, Assoc. Prof
Rahmi Ozdemir, MD
Timur Meşe, MD, Assoc. Prof

Acute rheumatic fever (ARF), a post-infectious systemic autoimmune disease, remains a major public health problem. It is the leading cause of acquired heart disease among children and young adults in developing countries. Carditis is the most important complication of rheumatic fever (RF) that is associated with permanent disability. An abnormal immune response to normal heart tissue, which is due to molecular mimicry between heart tissue antigens and streptococcal antigenic components, is the suggested mechanism in genetically susceptible individuals.

The electrocardiographic (ECG) findings of ARF have been well described. However, the relationship of these manifestations to carditis remains unknown. First-degree atrioventricular (AV) block is the characteristic conduction disturbance of RF. One-third of individuals have first-degree AV block, which can occur regardless of carditis. After inactivation of the disease, the PR interval can return to normal. Changes in ST segments and reduced-voltage QRS complexes may be found in the presence of pericarditis and pericardial effusion. In addition, increased QT and heart rate-corrected QT (QTc) dispersions that represent the heterogeneity of ventricular repolarisation and increased P-wave dispersions (PWd) were found in patients with acute rheumatic carditis (ARC).

In addition to the QT and QTc dispersions, the Tp-e interval, which on an ECG is the interval between the peak and the end of the T wave, can be used as an index of transmural dispersion of ventricular repolarisation (TDR). Both the Tp-e/QT and Tp-e/QTc ratios are also used as indices of ventricular repolarisation. Ventricular repolarisation in children with rheumatic carditis (RC) was previously evaluated using both QT and QTc dispersions. However, the novel repolarisation indices of Tp-e and Tp-e/QT have not been studied in RC patients previously. In this study, we aimed to assess the Tp-e interval and the Tp-e/QT ratio in children with RC, as well as investigate its relationship with inflammation and the number of valves involved.

Methods

Patients who were diagnosed with ARC between 2006 and 2016 at our centre were reviewed. Cases with insufficient data and those that did not fulfill the revised Jones criteria were excluded. Demographic features, complete blood count and erythrocyte sedimentation rate (ESR), as well as ECG and echocardiographic parameters at the time of diagnosis were collected from the patients’ data system. All echocardiographic examinations were performed by three paediatric cardiologists who are experienced in rheumatic heart disease and followed the guidelines of the American Society of Echocardiography and the European...
Society of Cardiology. The Vivid S6 Echocardiography System (General Electric Healthcare, Milwaukee, WI), which is equipped with an M4S-RS broadband transducer (General Electric Healthcare Japan Corporation, Hino-shi, Tokyo), was used for two-dimensional and colour-flow Doppler echocardiography. Apical and parasternal long-axis views were used to assess both mitral and aortic valve regurgitation.

The revised Jones criteria, which are suggested by the American Heart Association’s Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, were employed to differentiate pathological valve regurgitation from a normal state on the echocardiographic examinations. A regurgitation colour jet ≥ 2 cm in length for the mitral valve or ≥ 1 cm for the aortic valve, when seen in at least two planes with a peak velocity of > 3 m/s and persisting throughout systole (for mitral valve regurgitation) or diastole (for aortic valve regurgitation), was considered pathological. All the patients had moderate to severe carditis.

Oral steroid therapy was started on all patients, regardless of the severity of the carditis. Prednisolone (2 mg/kg/day) was given for two weeks and then tapered off. Aspirin was started at 80–100 mg/kg/day (maximum dose 3.5 g/day) to prevent rebound.

This study was approved by the local ethics committee. Oral steroid therapy was started on all patients, regardless of the severity of the carditis. Prednisolone (2 mg/kg/day) was given for two weeks and then tapered off. Aspirin was started at 80–100 mg/kg/day (maximum dose 3.5 g/day) to prevent rebound.

The data of 153 gender- and age-matched healthy control subjects were recorded from the same computerised database. This study was approved by the local ethics committee.

A standard 12-lead ECG was recorded at a speed of 25 mm/s and an amplitude of 1 mV/cm while the patients were lying in a supine position at the time of diagnosis. The ECG measurements of the PWd, QT, QTc and Tp-e intervals and the calculation of the QT and PW dispersions and Tp-e/QT were performed by the same blinded paediatric cardiologist. All durations were measured manually with calipers and a magnifying glass. The means of three measurements of the P wave, QT duration and Tp-e interval were used for further calculations. No significant discrepancy was present among the measurements. The intra-observer variance for each measurement was < 6%.

The PWd was calculated as the difference in duration between the Pmax and Pmin. The QT interval was determined as the distance between the beginning of the QRS wave and the end-point of the T wave with the isoelectric line. The QTc was calculated from these measurements.

Comparison of the ECG findings of the patients with one- or two-valve involvement was performed from precordial leads. The Tp-e/QT ratio was calculated from these measurements.

### Table 1. Demographic and electrocardiographic characteristics of patients with rheumatic carditis and healthy controls

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients (n = 139)</th>
<th>Healthy controls (n = 155)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>10.9 ± 2.4</td>
<td>11.7 ± 3.2</td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>83/56</td>
<td>73/80</td>
<td></td>
</tr>
<tr>
<td>PW dispersion (ms)**</td>
<td>40 (0–100)</td>
<td>20 (0–80)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>QT dispersion (ms)**</td>
<td>49 (20–100)</td>
<td>30 (10–60)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>QTc dispersion (ms)**</td>
<td>55 (15–120)</td>
<td>45 (5–110)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Tp-e (ms)**</td>
<td>95 ± 20</td>
<td>85.7 ± 18.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Tp-e/QTc</td>
<td>0.23 ± 0.04</td>
<td>0.22 ± 0.05</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Tp-e/QT</td>
<td>0.27 ± 0.06</td>
<td>0.26 ± 0.06</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

*Data are expressed as median (minimum –maximum).

### Table 2. Comparison of electrocardiographic findings of the patients with one- or two-valve involvement

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>One valve (n = 79)</th>
<th>Two valves (n = 60)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tp-e (ms)</td>
<td>93.5 ± 18.1</td>
<td>97.5 ± 22.2</td>
<td>0.25</td>
</tr>
<tr>
<td>Tp-e/QTc</td>
<td>0.22 ± 0.03</td>
<td>0.23 ± 0.04</td>
<td>0.43</td>
</tr>
<tr>
<td>Tp-e/QT</td>
<td>0.27 ± 0.05</td>
<td>0.28 ± 0.06</td>
<td>0.38</td>
</tr>
<tr>
<td>PW dispersion (ms)</td>
<td>43 ± 13.8</td>
<td>42.1 ± 16.5</td>
<td>0.66</td>
</tr>
<tr>
<td>QT dispersion (ms)</td>
<td>48.5 ± 15.6</td>
<td>45.5 ± 13.9</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD.

**Statistical analysis**

The SPSS 18.0 package program was used (SPSS Inc, Chicago, IL, USA) for statistical analysis. The distribution pattern of data was evaluated by the Shapiro–Wilk test and graphic methods. Values are expressed as either mean ± SD, median (minimum – maximum), or number (percentage) where appropriate. The Student’s t-test was used for normally distributed data. The Mann–Whitney U-test was used for abnormally distributed data. Notably, for more than two groups, we used one-way variance analyses and the Kruskal–Wallis test, respectively. Chi-squared analysis was used for the comparison of categorical variables.

The correlations between parameters were assessed using Spearman’s correlation test. The receiver operating characteristic (ROC) curve was applied to detect significant predictor cut-off values for the presence of myocardial involvement. A p-value < 0.05 was considered statistically significant.

### Results

A total of 174 patients were diagnosed with ARC between 2006 and 2016 at our centre. After the cases with insufficient data and those that did not fulfill the revised Jones criteria were excluded, the study included 139 patients with ARC. The median follow-up period was 4.6 years (range: six months to 8.5 years). No significant arrhythmic events or death were observed either at the time of diagnosis or during the follow-up period.

The demographic and ECG characteristics of the patients and healthy controls are listed in Table 1. Eighty-three patients were male and 56 were female. The mean age of the patients was 10.9 ± 2.4 years. The PWd, QTd and QTcd were significantly higher in patients with ARC compared to the healthy controls (all p-values < 0.001). The Tp-e interval, Tp-e/QT and Tp-e/QTc ratios were also significantly increased in ARC patients compared to the controls (p < 0.001, p < 0.05 and p < 0.05, respectively).

A QTd above 55 ms predicted the presence of myocardial involvement, with a sensitivity of 73% and a specificity of 98%. Analysis of the ROC curve for the QTd showed an area under the curve (AUC) of 0.76 (p < 0.001) (95% CI: 70–82).

A Tp-e interval above 85 ms predicted the presence of myocardial involvement, with a sensitivity of 56% and a specificity of 79%. Analysis of the ROC curve for the Tp-e showed an AUC of 0.80 (p < 0.001) (95% CI: 76–85).

Comparison of the ECG findings of the patients with one-mitral or aortic valve) and two-valve (both mitral and aortic valve) involvement was performed from precordial leads.
valve) involvement are shown in Table 2. Seventy-nine of the patients had one-valve and the remaining patients had two-valve involvement. There was no significant difference between the two groups in terms of PW and QT dispersions (all p-values > 0.05) and the Tp-e interval, Tp-e/QT and Tp-e/QTc ratios (all p-values > 0.05). When patients were evaluated in terms of correlation between acute-phase reactants and repolarisation indices, including white blood cell count, ESR, PWd, QTd and QTcd, Tp-e interval, and Tp-e/QT and Tp-e/QTc ratios, we found no correlation between these parameters (Table 3).

**Table 3. Correlation of electrocardiographic findings and acute-phase reactants**

<table>
<thead>
<tr>
<th>ESR (mm/h)</th>
<th>PWd</th>
<th>QTd</th>
<th>QTc</th>
<th>Tp-e</th>
<th>Tp-e/QTc</th>
<th>Tp-e/QT</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>-0.04</td>
<td>0.03</td>
<td>0.00</td>
<td>0.07</td>
<td>0.09</td>
<td>0.02</td>
</tr>
<tr>
<td>p</td>
<td>0.63</td>
<td>0.70</td>
<td>0.95</td>
<td>0.40</td>
<td>0.28</td>
<td>0.81</td>
</tr>
</tbody>
</table>

**Indices**: ESR, erythrocyte sedimentation rate; WBC, white blood cell count.

### Discussion

This study demonstrated that the P-wave, QT and QTc dispersions, Tp-e interval, and Tp-e/QT and Tp-e/QTc ratios were increased in patients with ARC. To the best of our knowledge, this study is the first to evaluate the parameters of transmural dispersion of repolarisation of the Tp-e interval, and Tp-e/QT and Tp-e/QTc ratios in a large number of patients with ARC.

Both the P-wave dispersion and the maximum P-wave durations are important non-invasive ECG indicators for assessing the homogenous distribution of sinus node impulses through the atrial myocardium. These parameters reflect the tendency of the atrial myocardium to have rhythm disturbances, such as atrial arrhythmias. Moreover, the Tp-e/QT ratio was found to be a more accurate indicator of ventricular arrhythmogenesis than the Tp-e interval and QTd because of its independence from a patient’s heart rate. Some researchers have found that both QTd and QTcd were higher in patients with ARC, and they have also stated that QTd was associated with the severity of valvular regurgitation.

In previously reported studies, increased transmural dispersion of repolarisation was found to be correlated with increased inflammatory activity. It was reported that TDR is increased in patients with ankylosing spondylitis and familial Mediterranean fever, however, valvular regurgitation is the leading determinant of prognosis in patients with ARC. Myocardial involvement is a well-known manifestation of RC. Therefore, myocardial involvement may cause the heterogeneity of repolarisation in children with ARC.

In our study, in addition to the QTd and QTcd, we evaluated the novel markers of TDR in the Tp-e interval, and Tp-e/QT and Tp-e/QTc ratios in ARC patients; these parameters were all found to be higher in the ARC group. To our surprise, we found no correlation between TDR and the number of valves involved. We also found no correlation between the acute-phase reactants and QTd, QTcd, Tp-e interval, and Tp-e/QT and Tp-e/QTc. It may be that the increase in TDR and myocardial involvement occurred as an all-or-none phenomenon in our patients. Our results indicate that the heterogeneity of TDR occurs independently from the severity of acute inflammation and the number of valves involved.

### Study limitations

Our study had certain limitations, with the retrospective design being the primary one. We did not evaluate the correlation between the degree of valvar involvement and the TDR parameters. In addition, we could not follow up with the study population prospectively for ventricular arrhythmic episodes. Therefore, we could not assess the TDR parameters regarding...
Conclusions

This study showed that the new TDR parameters: Tp-e interval, Tp-e/QT ratio and QTd were increased in children with ARC; however, the heterogeneity of TDR seems to occur independently of acute inflammation and the number of valves involved. The prolonged Tp-e interval and increased Tp-e/QT ratio might be useful markers for predicting myocardial involvement in children with ARC. These parameters may be used as minor criteria in RF. Therefore prospective follow-up studies are needed to evaluate TDR parameters in children with RC, both before and after treatment.

References