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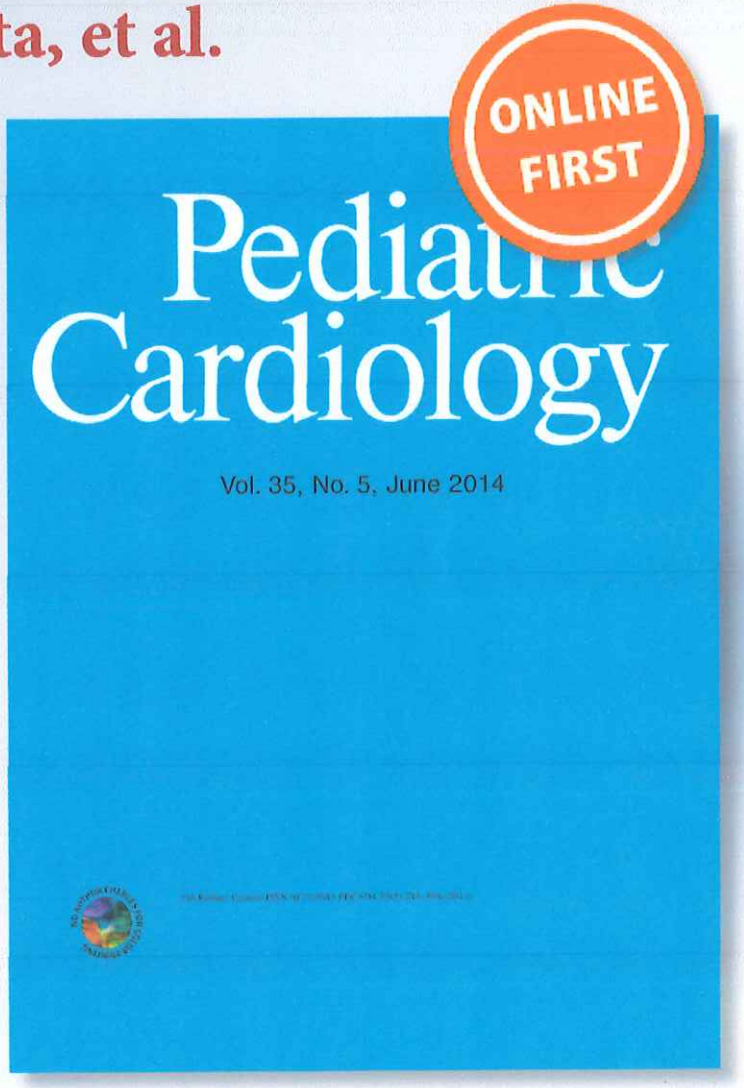

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ORIGINAL ARTICLE

Inflammation Aggravates Heterogeneity of Ventricular Repolarization in Children With Kawasaki Disease

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Abstract Kawasaki disease complicates with myocarditis and vasculitis. Even if myocarditis is asymptomatic, heterogeneity of ventricular repolarization may be increased in the acute phase. We evaluated whether the change in repolarization characteristics can be used as a predictor for myocarditis and coronary lesions. Enrolled 34 children who were treated with intravenous immunoglobulin therapy. There were no sequelae in the recovery phase in any subjects, including those who had transient coronary artery lesion. QT and the interval from the Tpeak to Tend (Tp-e) were determined. The Tp-e/QT ratios were compared between the acute and recovery phases and correlations with CRP level and body temperature were evaluated. A retrospective evaluation of Tp-e/QT as predictors of coronary dilation was also performed. Tp-e/QT in the acute phase correlated positively with body temperature and CRP level. In a comparison of patients with and without transient coronary artery lesion, Tp-e/QT was significantly higher in those with dilation. In conclusion, Tp-e/QT was strongly related to transient coronary dilation, in comparison with inflammatory indicators including fever and CRP level.

Keywords Kawasaki disease · Ventricular repolarization heterogeneity · Tpeak to Tend interval · Tp-e/QT ratios

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Introduction

Kawasaki disease (KD) is an acute febrile illness of unknown origin that causes systemic vasculitis and myocarditis and coronary dilation. Children with coronary artery aneurysm as a sequela have increased heterogeneity of ventricular repolarization due to ischemic myocardial damage [5, 18].

Evaluation of arrhythmogenicity in the acute phase is important for the treatment and management of KD. However, few comparative studies have investigated ventricular repolarization changes in the acute phase, and derangements in ventricular repolarization associated with inflammation have not been sufficiently examined. We used electrocardiogram (ECG) analysis to examine the relationship of repolarization characteristics with coronary lesions and myocarditis [10].

In the current study, Tp-e/QT, a parameter that reflects the heterogeneity of global ventricular repolarization, was estimated by body surface ECG in the acute phase of KD and in the recovery phase after immunoglobulin therapy. The relationships of Tp-e/QT with body temperature and biochemical data related to severity were examined, and Tp-e/QT was evaluated as a predictor of cardiovascular complication.

Subjects and Methods

The study subjects were 40 children with KD hospitalized at University Hospital from January 2008 to January 2011. After the diagnosis had been determined, all the patients had fulfilled the American Heart Association guidelines for the diagnosis of KD [17] and received intravenous immunoglobulin (2 g/kg) treatment 5.4 ± 1.3 days after the onset of fever. In addition, aspirin was given at a dose of 50 mg/kg/day for the first 5–10 days followed by a lower antiplatelet dose (5 mg/kg) for the next 4–6 weeks.

Three patients were excluded from the current analysis because stable ECG recordings were not possible due to vigorous motion and crying. An additional three patients were excluded because they showed extremely high heart rates (HRs > 180 bpm), with overlapping of the T-wave terminal portion and the P-wave.

Finally, 34 patients (22 boys and 12 girls, age 2.1 ± 1.9 years) were included in this study. The enrolled patients had sufficient records of echocardiography and electrocardiography at the same time in the acute and recovery phases. The mean fever duration was 7.2 ± 3.1 days, and the mean body temperature in the acute phase was 37.6 ± 1.4 °C. The mean hospital stay was 17.2 ± 5.4 days.

All the children underwent at least two echocardiography examinations by the same observer, first at the time of initial admission and the second at the follow-up visit 3–4 weeks later. Dilation of the right coronary artery and left anterior descending coronary artery was defined according to the American Heart Association criteria as a *z*-score of 2.5 or higher (with standard deviation units from the mean internal diameter normalized for body surface area) [17]. Transient coronary artery lesion in the left anterior descending coronary artery was found in eight patients and no lesion in right coronary artery, but all cases resolved in the recovery phase.

An equal number of healthy children ($n = 34$, age 2.2 ± 0.4 years) matched in age and sex with the study subjects were used as healthy control subjects. This study was approved by our institution's Ethics Committee for epidemiologic and clinical research.

After obtaining written informed consent from the subjects and their parents or guardians, ECG (CM5 lead) was performed using a biopolygraph recorder (MP-150; Biopac Systems, Inc., Goleta, CA, USA) during echocardiography. Tricloryl syrup (0.7 ml/kg) was preadministered to children ages 3 months to 1 year for sedation.

The ECGs were stored on disk by an independent investigator blinded to the patient data. The first differential and absolute function in the ECG recording for 120 continuous heart beats without arrhythmia were obtained with analysis software (Acqknowledge, version 3.9, Biopac Systems Inc.) and used to determine the RR interval, Q-wave start, and T-wave end. The QT interval and the interval from the T-wave peak to the T-wave end (Tp-e interval) were automatically determined [10]. The QT and Tp-e intervals were corrected by Fridericia equation to give the QTc and Tp-eC intervals, respectively. Then, Tp-e/QT, the characteristic ratio of ventricular repolarization, was estimated.

The Tp-eC interval and Tp-e/QT were compared between the acute phase (day of illness: 5.7 ± 1.2 days after onset) and the recovery phase (22.0 ± 4.1 days after onset). The relationships of the Tp-eC interval and Tp-e/QT to biochemical data at admission and the body temperature at echocardiography also were examined. The biochemical data included leukocytes, hematocrit, platelets, aspartate aminotransferase (AST), sodium, potassium, chloride, total protein, albumin and C-reactive protein (CRP).

Statistical analysis was performed using JMP Statistical Analysis Software, version 5.1.2 (SAS Institute Inc., Cary, NC, USA). No subject needed heart failure treatment including catecholamines and diuretics, and there were no drug effects on the QT interval. An intergroup (acute phase, recovery phase, and healthy control subjects) comparison was performed using analysis of variance (ANOVA) and a Tukey–Kramer honestly significant difference test for pairwise comparisons. Values of p lower than 0.05 were considered statistically significant.

Correlations of the biochemical data with the Tp-eC interval and Tp-e/QT were evaluated by ANOVA and simple linear regression analysis. A Wilcoxon Chi square test was used to compare Tp-e/QT between groups with and without transient coronary artery lesion. A p value lower than 0.05 was considered significant in all analyses. A receiver operating characteristic (ROC) curve was constructed to identify a Tp-e/QT cutoff value for predicting a transient coronary artery lesion.

Results

The changes in ECG parameters are shown in Table 1. The findings showed significant differences in the mean heart rate, the RR interval, and the QTc interval between the acute and recovery phases. The repolarization characteristics showed no significant differences between the acute and recovery phases in terms of Tp-e or Tp-eC interval. In contrast, Tp-e/QT significantly increased in the acute phase.

Table 1 Electrocardiogram parameters in the acute and recovery phases

Parameters	Acute phase	Recovery phase	*p* value
HR (bpm)	131.06 ± 28.7	109.5 ± 12.1	<0.05
RR (ms)	477.5 ± 110.5	562.9 ± 63.0	<0.05
QT (ms)	301.2 ± 39.3	304.8 ± 23.9	0.593
QTc (ms)	358.2 ± 34.2	383.8 ± 24.5	<0.05
Tp-e (ms)	68.9 ± 15.6	66.9 ± 7.4	0.737
Tp-eC (ms)	88.8 ± 19.5	81.6 ± 8.4	0.961
Tp-e/QT	0.25 ± 0.05	0.21 ± 0.02	<0.05

Comparisons of the HR (bpm), the mean RR interval (RR), the mean QT interval (QT), the corrected QT interval (using Fridericia's formula), and Tp-e (Tpeak to Tend interval), Tp-eC (corrected Tp-e using Fridericia's formula), and Tp-e/QT (ratio of Tp-e to QT interval) in the acute and recovery phases are shown. Each value is expressed as the mean ± SD

HR heart rate

Table 2 Blood biochemistry data in the acute and recovery phases

	Acute phase	Recovery phase	*p* value
WBC (10^2/mm^3)	129.8 ± 53.6	83.0 ± 32.5	<0.05
Hematocrit (%)	33.3 ± 3.4	34.5 ± 2.9	<0.05
Platelet (10^4/mm^3)	35.7 ± 14.7	44.4 ± 13.4	<0.05
AST (IU/l)	58.7 ± 80.0	40.0 ± 15.6	0.901
Sodium (mmol/l)	134.4 ± 3.2	136.5 ± 2.1	<0.05
Potassium (mmol/l)	4.5 ± 0.5	4.5 ± 0.4	0.924
Chloride (mmol/l)	98.9 ± 3.5	102.2 ± 1.4	<0.05
Total protein (g/dl)	6.8 ± 0.5	8.5 ± 0.5	<0.05
Albumin (g/dl)	3.7 ± 0.4	3.8 ± 0.5	0.325
CRP (mg/dl)	7.6 ± 5.2	0.3 ± 0.1	<0.05

Comparisons of WBC, hematocrit, platelets, AST, sodium, potassium, chloride, total protein, albumin, and CRP in the acute and recovery phases are shown. Each value is expressed as the mean ± SD

WBC white blood cell count, *AST* aspartate aminotransferase, *IU* international units, *CRP* C-reactive protein

In the comparison of biochemical data between the acute and recovery phases, significant differences were found in leukocytes, hematocrit, platelets, sodium, total protein, and CRP but not in AST, potassium, chloride or albumin (Table 2). In linear regression analysis, Tp-e/QT had significant positive correlations with body temperature ($r = 0.567$; $p = 0.0005$) and CRP level ($r = 0.484$; $p = 0.003$) (Fig. 1).

Figure 2 shows typical ECG patterns from a patient in the acute and recovery phases. The heart rate was much the same, and the acute-phase ECG had a steeper slope of the ascending limb of the T-wave.

Biochemical data, Tp-e/QT, and Tp-eC in the acute phase were compared between patients with and without transient coronary artery lesion. Those with a transient coronary artery lesion had a significantly higher Tp-e/QT (0.287 ± 0.054 vs. 0.238 ± 0.049; $p = 0.026$). Averaged ratios were significantly decreased from the acute phase to

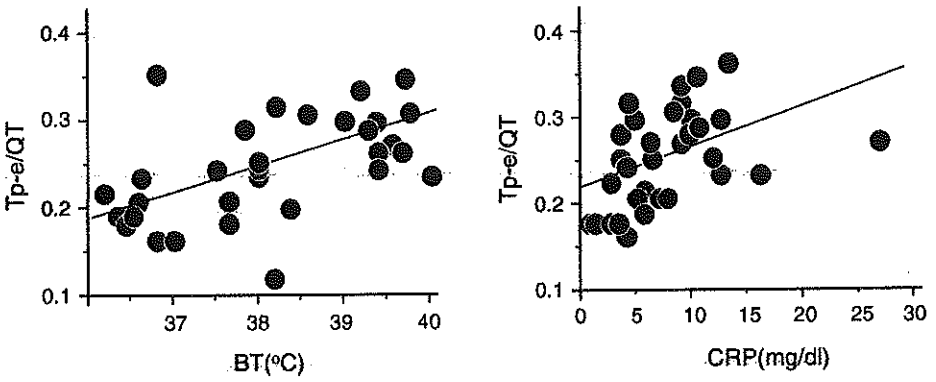

Fig. 1 Relationship between Tp-e/QT and body temperature or C-reactive protein (CRP) in the acute phase. The body temperature and Tp-e/QT values show a significant positive linear correlation ($r = 0.567$; $p = 0.0005$). Furthermore, the CRP values and Tp-e/QT values show a significant positive linear correlation ($r = 0.484$; $p = 0.0037$). *BT* body temperature (°C)

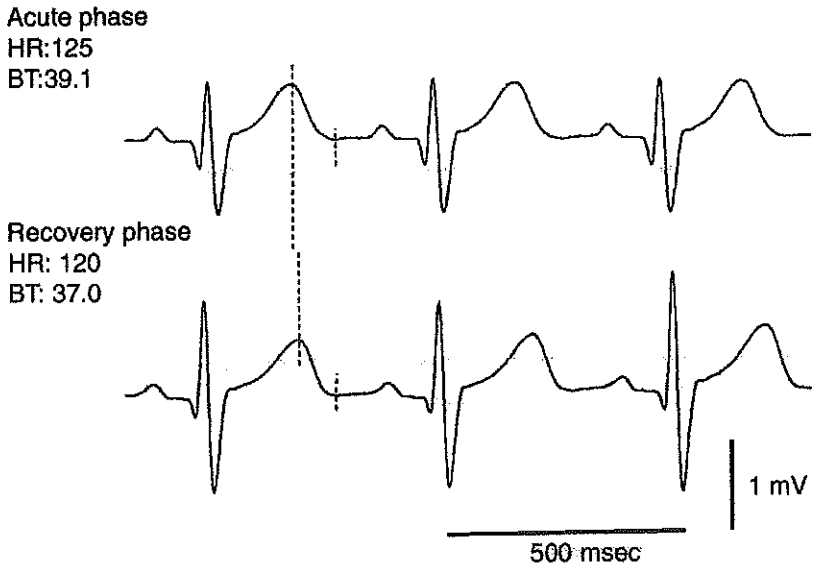

Fig. 2 Typical electrocardiographic (ECG) traces were recorded during the acute and recovery phases in a 4-year-old boy with Kawasaki disease. Three of the 120 measured heartbeats are shown as representative heartbeats. The *upper trace* showed a *steeper slope* of the ascending limb of the T-wave. Comparisons of QT interval, Tp-e, and Tp-e/QT (acute vs. recovery: 316.7 vs. 307.0 ms, 100.9 vs. 71.1 ms, 0.318 vs. 0.232 ms, respectively) are shown. *Dot lines* (Tpeak and Tend) were determined by the first differential and absolute function. *HR* heart rate, *BT* body temperature (°C)

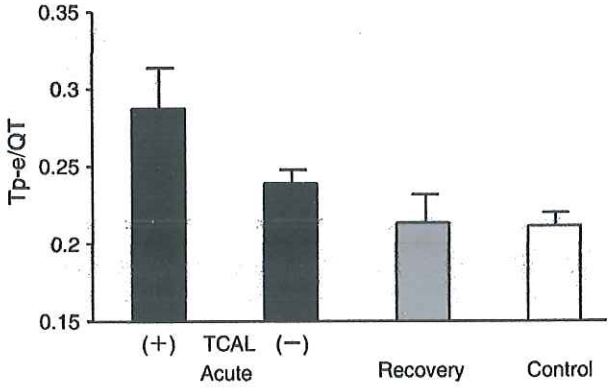

Fig. 3 Tp-e/QT values with and without transient coronary artery lesion in the acute phase, recovery phase, and healthy control subjects. Comparisons of Tp-e/QT ($p < 0.05$ for the acute phase with TCAL vs. all others, $p < 0.05$ for the acute phase without TCAL vs. all others, and $p < 0.05$ for the acute phase vs. healthy control subjects: 0.25 ± 0.05 vs. 0.21 ± 0.02). No statistically significant difference was found between the recovery phase and the healthy control subjects. *TCAL* transient coronary artery lesion; (+) with TCAL, (−) without TCAL. *Acute* acute phase of Kawasaki disease (KD); *Recovery*, recovery phase of KD; *Control*, healthy control subjects

the recovery phase (-0.60 ± 0.54 to -1.22 ± 0.31; $p < 0.05$) and then restored to a value equivalent to that of the healthy control subjects (Fig. 3). The ROC curve analysis showed that the optimal cutoff value for predicting transient coronary artery lesion was 0.282, with a sensitivity of 75 %, a specificity of 85 %, and an area under the ROC curve of 0.728.

Discussion

The results of this study showed that Tp-e/QT is significantly higher in children with KD in the acute phase than in the recovery phase, indicating increased heterogeneity of ventricular repolarization. In the acute phase, Tp-e/QT also was significantly higher in children with transient coronary artery lesion.

Kawasaki disease is a systemic vasculitis of unknown origin that occurs mainly in children younger than 5 years. The incidence of the most important complication of coronary artery aneurysm has decreased due to high-dose intravenous immunoglobulin, but coronary lesions still are found in about 10 % of children [14, 16]. The severity of KD and transient coronary artery lesion cannot be predicted from laboratory values such as the leukocyte count and the CRP level, so various scores to predict severity have been proposed [9].

The Tp-e/QT parameter defines the relationship between the heterogeneity of cardiac repolarization (Tp-e interval) and the repolarization QT interval [7]. Clinical studies investigating the heterogeneity of ventricular repolarization have shown that Tp-e/QT is useful for evaluating arrhythmogenic substrates in patients with myocardial infarction and hypertrophic cardiomyopathy or Brugada syndrome [3, 4, 11, 19].

A recent study investigating the long-term prognosis of patients with coronary disease showed a prolonged Tp-e interval in cases with sudden cardiac death compared with a nonaccident group [19]. Thus, analysis of the ventricular repolarization interval and evaluation of repolarization based on Tp-e/QT are of interest. The Tp-e interval and Tp-e/QT currently are considered to be indicators of the variation in total (whole heart) repolarization because the Tp-e interval includes repolarization at spatially different sites and not just the local potential [2].

Based on these findings, we designed a study to evaluate panmyocarditis due to KD using Tp-e/QT as an indicator for abnormal repolarization of the whole heart due to inflammation. We found that Tp-e/QT in the acute phase was significantly higher than in the recovery phase. Biochemical data did not suggest an effect of electrolytes on Tp-e/QT, but Tp-e/QT had significant positive correlations with body temperature and the CRP level.

Fever due to inflammation results from release of various cytokines, with a particular relationship of interleukin-6 (IL-6) with CRP [21]. Cytokines including TNF-α and interleukins are increased in the acute phase of KD and induce systemic inflammation [12, 13, 20]. These cytokines modulate Ca^{2+} and K^{+} currents that act in ventricular repolarization. Tumor necrosis factor alpha (TNF-α) decreases the K^{+} current, resulting in prolonged repolarization, whereas IL-1β enhances Ca^{2+} release from the sarcoplasmic reticulum and deteriorates intracellular Ca^{2+} regulation. Furthermore, the distribution of ion channels in myocardial cells depends on the heart site. Therefore, the effects of cytokines may increase the heterogeneity of repolarization in the whole heart [1, 6, 8]. Thus, characteristic values of ventricular repolarization in the fever phase are likely to be changed by the humoral regulatory factor.

Our results show that Tp-e/QT is useful for evaluating inflammation and the severity of vasculitis and myocarditis associated with KD. In the future, we should examine the use of Tp-e/QT for pathologic evaluation in more subjects, with the goal of developing a diagnostic and therapeutic strategy.

Study Limitations

This study had several limitations. First, the number of patients included in this study was small. However, data from noninvasive examination were rare and potentially

useful for managing KD. Second, it was difficult to analyze the QT interval automatically in an ECG recording with a high heart rate (>180 bpm), in which the T-wave end overlapped the ascending limb of the P-wave.

Third, Muniz et al. [15] recently reported that mean coronary artery dimensions in children with non-KD febrile illnesses were larger than in afebrile subjects, suggesting that the coronary artery in children with a febrile illness, whatever the etiology, could be prone to dilation and that electrocardiographic changes might occur together with a febrile illness. Therefore, febrile patients without KD should have been included in this study as control patients, but we did not plan to include such patients at the time the study was designed.

Conclusion

The characteristics of ventricular repolarization in the acute and recovery phases of KD were evaluated using Tp-e/QT. In the acute phase, Tp-e/QT was high, indicating increased heterogeneity of ventricular repolarization and suggesting an effect of humoral regulatory factor on fever and CRP. These data suggested that Tp-e/QT was more useful than CRP and body temperature for predicting complications, including transient coronary artery lesion and myocarditis.

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