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Increased QT Interval Dispersion is Associated with Coronary Artery Involvement in Children with Kawasaki Disease

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ABSTRACT

Objectives: Coronary artery (CA) involvement is the most well known complication of Kawasaki disease (KD). Previous studies have suggested that QT dispersion has a predictive value in diagnosing cardiac ischemia, ventricular arrhythmia, and sudden cardiac death. However, limited data exits regarding the application of QT dispersion in KD. Therefore, we sought to determine whether there is a relationship between QT dispersion and CA involvement in patients with KD. ***Methods***: We performed a cross-sectional study of all consecutive patients with KD who were followed-up at the Pediatric Rheumatology Department (Pediatrics Center of Excellence affiliated to Tehran University of Medical Sciences, Tehran, Iran) from September 2013 to November 2015. Patients who met the criteria for KD, based on the American Heart Association guideline, were enrolled in the study. We collected data regarding patients' demographics, clinical manifestations, laboratory, and echocardiographic findings. ***Results:*** A total of 70 KD patients were identified, including 43 males (61.4%) and 27 females (38.6%). The median age of patients was 21.0 (11.0–48.0) months. We found statistically significant differences between age, gender, and platelet count among patients with and without CA involvement ($p < 0.050$). Median corrected QT dispersion in patients with CA involvement calculated from 12 leads in the acute phase was significantly higher compared to the non-CA involvement group (108.0 (89.5–138.5) ms vs. 63.0 (54.0–74.5) ms, respectively ($p < 0.001$)). ***Conclusions:*** Prolonged QT dispersion (corrected or non-corrected) during the acute and convalescence phases in patients with KD is associated with coronary involvement.

Kawasaki disease (KD) is characterized by an acute febrile, self-limited, generalized multisystem vasculitis that typically affects children aged less than five years.[1] The underlying etiology of KD remains unclear. Nonetheless, epidemiological studies suggest that asymptomatic or non-vasculitis infection agents in genetically susceptible individuals could play a role in KD's pathogenesis.[2,3] Patients with KD will develop a variety of clinical manifestations. However, the most important clinical feature is cardiovascular sequels including coronary artery (CA) aneurysm (which occurs in almost 25% of untreated cases), myocardial infarction, arrhythmias, and cardiomyopathy with depression of myocardial contractility.[1,4–6] A delay in diagnosis and initiation of appropriate treatment will result in more undesirable outcomes, such as the increased risk of CA aneurysm.[7] In addition, injury to myocardial tissue due to excessive inflammation can cause an altered electrical impulse propagation, which manifests through the regional heterogeneity of QT interval duration in myocardial recovery times.[8] This inter-lead differences on standard 12-lead electrocardiogram (ECG) is termed QT dispersion.[9] Several studies have demonstrated that increase in QT dispersion has an important predictive value for developing potentially lethal arrhythmias and CA aneurysms.[10–16] However, the association between QT dispersion and CA involvement among patients with KD has not been widely studied. Therefore,

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we sought to assess the role of QT dispersion as a practical diagnostic tool for detecting cardiac involvement among patients with KD.

METHODS

We conducted a cross-sectional study including all consecutive KD patients who were followed-up at the Pediatric Rheumatology Department (Pediatrics Center of Excellence affiliated to Tehran University of Medical Sciences, Tehran, Iran) between September 2013 and November 2015. A total of 70 patients who met the criteria for KD, based on the American Heart Association guideline, were enrolled in the study.[17] The definition for CA involvement was based on the following criteria including abnormal coronary arteries if the internal lumen diameter was > 3 mm in children < 5 years old or > 4 mm in children ≥ 5 years old; if the internal diameter of a segment measured ≥ 1.5 times that of an adjacent segment; or if the coronary lumen was clearly irregular.[18] Patients were excluded if they had other causes of cardiac involvement except for CA disease.

We collected data regarding patients' demographics, clinical manifestations, laboratory, and echocardiographic findings. After diagnosis of KD, all patients received 2 g/kg of intravenous immunoglobulin as a single and high dose of aspirin (80–100 mg).

The ethics committee of Tehran University of Medical Science approved the study and all parents completed an informed consent form before all procedures were performed. The study was conducted following the Declaration of Helsinki and other applicable guidelines, laws, and regulations.[19]

For each patient, 12-lead ECG at a speed of 25 mm/sec were recorded during the acute phase of the disease. ECG was done on Fokuda (Japan) machine. The QT interval was calculated from the beginning of the QRS complex to the end of the T wave. The end of T wave was defined as the point at which return to baseline, and if the U wave was identified it was excluded from the QT. In cases where the T wave could not be reliably measured, the data was excluded from the study. The QT dispersion was measured as the difference between the maximum and the minimum QT intervals for any of the 12-leads ECG of each patient. The calculation of the corrected QT (QTc) interval was done using the Bazzet's formula (QTc = QT/square root of the RR interval).[20]

Continuous variables were examined for a normal distribution using the Shapiro-Wilk test. We used the *t*-test for independent numeric variables, and for independent nominal variables, Fisher's exact test or Mann–Whitney's U test were used, respectively. Pearson's correlation analysis was used to evaluate the relationship between QTc dispersion and other parameters. We evaluated the suitability of different QTc dispersion for distinguishing between patients with and without CA involvement according to receiver operating characteristic (ROC) curves. The area under the ROC curve (AUC) was calculated with 95% confidence intervals (CI). The cut-off values were defined in line with the optimal sensitivity and specificity. Statistical significance was defined as $p < 0.050$. Data were analyzed using SPSS Statistics (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.).

RESULT

A total of 70 KD patients were identified, including 43 males (61.4%) and 27 females (38.6%). Table 1 describes the baseline demographic and biochemical data of the study cohort. The median age of patients was 21.0 (11.0–48.0) months. The male to female ratio was 1.5:1. We found statistically significant differences between age, gender, and platelet count among patients with and without CA involvement ($p < 0.05.0$). Median QTc dispersion in patients with CA involvement calculated from 12-lead ECG in the acute phase was 108.0 (89.5–138.5) ms compared to 63.0 (54.0–74.5) ms in the non-CA involvement group ($p < 0.001$).

CA abnormality developed in 37 (52.9%) patients, including 15 subjects with small aneurysms (< 5 mm), 16 with medium aneurysms (5–8 mm), and six with giant aneurysms (> 8 mm). A post hoc analysis was implemented to compare between QTc dispersion and various degrees of the severity of CA. The results showed that the mean QTc dispersion was 141.0±62.2, which was significantly higher in patients with medium-sized aneurysms compared to other complications ($p < 0.001$).

QTc dispersion in both acute and convalescence phases was significantly higher in male subjects compared to females ($p = 0.017$ and $p = 0.042$, respectively) [Figure 1 and 2]. Moreover, the Pearson correlation showed that there was a

Table 1: Clinical characteristics and comparison between patients with and without coronary artery involvement.

Parameters	Total	With coronary involvement (n = 37)	Without coronary involvement (n = 33)	*p*-value*
Age, months	21.0 (11.0–48.0)	15.0 (6.5–48.0)	30.0 (18.0–50.0)	0.020
Sex				0.036
Male, n (%)	43 (61.4)	27 (73.0)	16 (48.5)	
Female, n (%)	27 (38.6)	10 (27.0)	17 (51.5)	
Platelet count, × 10^3 µL	560.0 (417.0–722.0)	653.0 (494.0–1010.0)	458.0 (376.0–601.0)	0.001
CRP	61.0 (34.0–130.0)	68.0 (36.0–145.0)	53.0 (33.0–118.0)	0.458
ESR	80.5 (54.2–102.7)	76.0 (52.1–104.5)	81.0 (58.5–103.5)	0.791
QTc dispersion, ms				
Acute phase	78.5 (60.7–115.0)	108.0 (89.5–138.5)	63.0 (54.0–74.5)	0.001
Convalescence phase	64.0 (49.7–141.2)	139.0 (74.5–209.0)	50.0 (43.0–63.0)	0.001

Data presented as interquartile range with 25th and 75th percentiles.
CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; QTc: corrected QT.
p-values < 0.050 were considered significant.
**The between-group comparison was made using Mann–Whitney's U test.*

significant positive correlation between QTc dispersion (both acute and convalescence phases) and CA involvement (r = 0.591, p < 0.001 and r = 0.669, p < 0.001, respectively). However, no significant correlation was observed between QTc dispersion and inflammatory markers such as erythrocyte sedimentation rate and C-reactive protein [Table 2 and 3].

The ROC curve was applied to determine the cut-off values for QTc dispersion in the acute phase with the best sensitivities and specificities for diagnosing CA involvement [Figure 3]. The area under the ROC

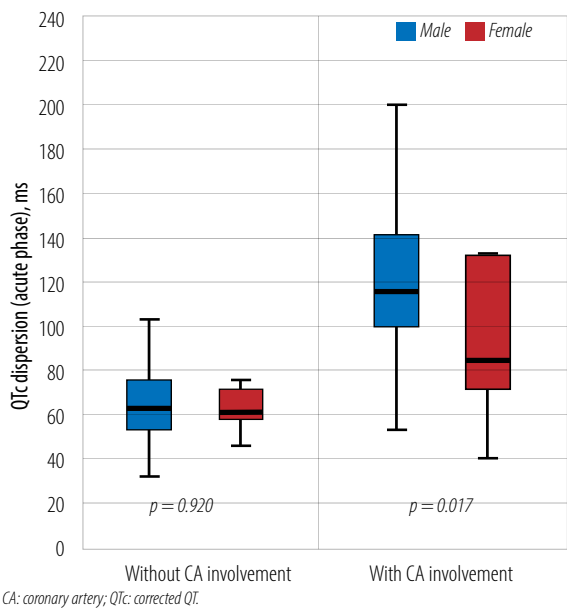


Figure 1: Association between QTc dispersion in the acute phase and CA involvement based on gender. The boxes represent the interquartile range, with the upper and lower edges of the boxes representing the 75th and 25th percentiles, respectively. The central horizontal lines within the boxes represent the median levels for each group.

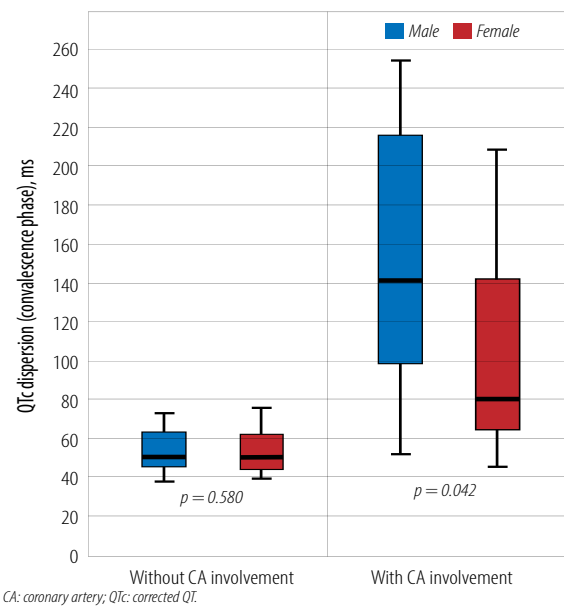


Figure 2: Association between QTc dispersion in the convalescence phase and CA involvement based on gender. The boxes represent the interquartile range, with the upper and lower edges of the boxes representing the 75th and 25th percentiles, respectively. The central horizontal lines within the boxes represent the median levels for each group.

Table 2: Correlation between corrected QT dispersion (acute phase) and clinical and laboratory parameters.

Parameters	*r*-value	*p*-value
Age	0.170	0.160
Gender	-0.319	0.007*
Platelet	0.160	0.186
CRP	0.099	0.414
ESR	-0.087	0.472
Coronary artery involvement	0.591	< 0.001*

** Statistically significant.*
CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

Table 3: Correlation between corrected QT dispersion (convalescence phase) and clinical and laboratory parameters.

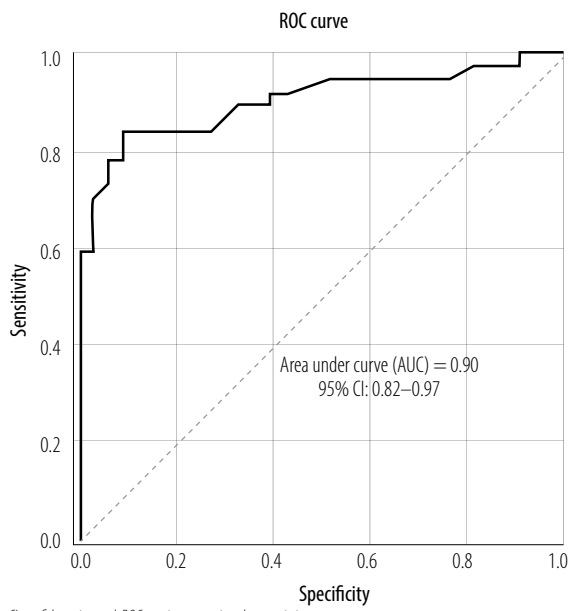
Parameters	*r*-value	*p*-value
Age	-0.195	0.106
Gender	-0.335	0.005*
Platelet	0.176	0.144
CRP	-0.009	0.944
ESR	-0.094	0.440
Coronary artery involvement	0.669	< 0.001*

** Statistically significant.*
CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

curve was 0.90 (95% CI: 0.82–0.97), indicating excellent diagnostic accuracy. A cut-off value of 76.5 ms was obtained for QTc dispersion in the acute phase, which gave a sensitivity of 83.8% and a specificity of 80.1%. The AUC for QTc dispersion in the convalescence phase was 0.90 (95% CI: 0.83–0.97), with a cut-off value of 63.5 ms (sensitivity of 83.8% and a specificity of 85.2%) [Figure 4].

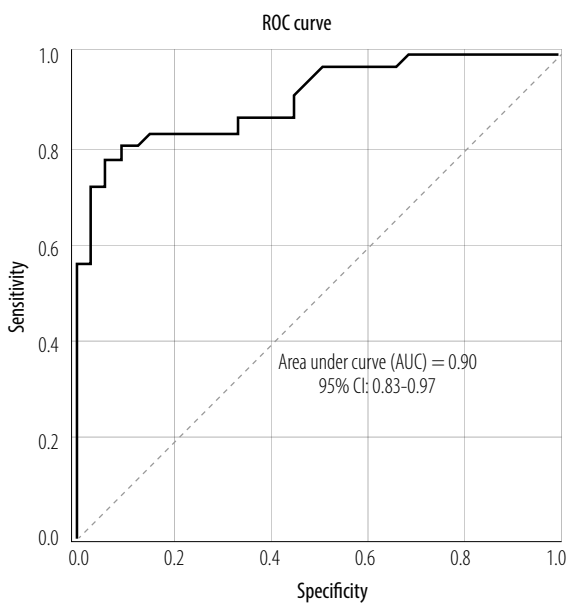
DISCUSSION

KD is an acute, self-limited vasculitis and cardiac involvement may occur in untreated cases. The development of CA aneurysm will lead to flow stasis and formation of thrombosis, which could eventually result in myocardial ischemia and infarction. The initial assessment of such complications are evaluated by echocardiography since it is an available and feasible diagnostic tool. Although most patients functional and structural measurements on initial echo may remain unaltered, it cannot detect all types of heart conditions or predict future heart problems.[21] Since the recognition of QT dispersion as a prognostic value for heart failure by Barr et al. in 1994[22], numerous studies have been examined the application of QT dispersion in different



CI: confidence interval; ROC: receiver operating characteristic.

Figure 3: ROC analysis was performed to calculate the AUC, sensitivity, and specificity of the QTc dispersion in the acute phase. The optimal cut-off value for QTc dispersion was 76.5 ms (sensitivity = 83.8% and specificity = 80.1%).



CI: confidence interval; ROC: receiver operating characteristic.

Figure 4: ROC analysis was performed to calculate the AUC, sensitivity, and specificity of the QTc dispersion in the convalescence phase. The optimal cut-off value for QTc dispersion was 63.5 ms (sensitivity = 83.8% and specificity = 85.2%).

medical disciplines.[23–26] QT dispersion reflects the heterogeneity of myocardial repolarization that can predict the incidence of ventricular arrhythmia, cardiomyopathy, and sudden cardiac death in both children and adults.[15,27,28]

The exact underlying mechanism of increased QT dispersion in KD is still unclear. However, two possible explanations for this difference in myocardial recovery times could be suggested. First, the increased QT dispersion may be due to the effect of an abnormal autonomic nervous system described by Kikuchi et al.[29] They demonstrated that in KD patients with cardiac involvement, vagal nerve activity was depressed, and therefore resulted in a loss of myocardial stabilization and increased the likelihood of the occurrence of malignant ventricular arrhythmia. Therefore, diminished vagal tone will result in increasing the resistance of peripheral blood flow and subsequently the increase in oxygen demand of the myocardium and may explain the prolongation of the QT interval due to myocardial ischemia. Notably, the current study demonstrated that QT dispersion and QTc dispersion in both the acute and convalescence phases of KD were significantly higher in patients with CA involvement compared to those with no CA involvement. This finding was similar to previous studies, indicating that electrocardiographic depolarization and repolarization would be prolonged in patients with CA involvement.[30–32] Moreover, QT dispersion was significantly correlated with CA involvement in our series. However, these findings were in disagreement with previously reported series indicating that no correlation exists between QT interval and CA involvement.[11]

Secondly, another possible cause of an increased QT dispersion may be related to early pathophysiological changes in the cardiovascular system. Since KD is a multi-systemic vasculitis that affects mostly small and medium-sized arteries, microcirculation disturbances could occur at the coronary microcirculation level even in the absence of endocardial and pericardial alterations. Pathological and clinical evidences suggest that myocardial fibrosis may develop as a result of previous ischemia in the area perfused by the CA.[33] Thus, the presence of small areas of myocardial fibrosis may alter the time course of ventricular repolarization, manifested by the existence of dispersion in the effective refractory period.

Previous studies have shown that in patients with primary systemic vasculitides such as systemic lupus erythematosus, Churg-Strauss syndrome, and Behçet's disease, QT dispersion is associated with cardiovascular involvement.[10,25,34–36] Thus, it should be noted that ECG is an essential component of the cardiovascular assessment and measuring QT dispersion could be used as a reliable prognostic test modality for diagnosis of cardiac inflammatory involvement, such as pericarditis, myocarditis, and coronary arteritis, similar to that in KD.[37]

A previous study reported that the optimal cut-off value of QT dispersion in patients with KD was > 60 ms dispersion with a higher sensitivity in detecting severe coronary aneurysms.[31] In contrast, the optimal cut-off value obtained in our study for corrected QT dispersion both in the acute and convalescence phases was 76.5 ms and 63.5 ms, respectively, suggesting that the optimal cut-off value of QTc dispersion with KD is higher than that previously reported. Our results confirmed that the cut-off values differed between the two phases of KD, indicating that different causative mechanisms might account for the prolongation of QTc dispersion in the respective diseases.

The major limitation of our study was its relatively small sample size and the cross-sectional nature of the data. Although our study has achieved a promising result in the application of QT dispersion for early detection of cardiac involvement, whether our findings can be safely extrapolated to all patients with KD should be investigated in a large, prospective, and multicenter study.

CONCLUSION

Prolonged QT dispersion (corrected or non-corrected) during the acute and convalescence phases in patients with KD is associated with coronary involvement. However, no statistically significant correlation was observed between the repolarization changes and inflammatory markers or disease severity.

Disclosure

The authors declared no conflict of interest. This research was part of a Pediatric Residency thesis (of Dr. L. Hamzehlou) and was approved and financially supported by a grant from Tehran University of Medical Sciences (No: 92-11-165-5006).

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