ORIGINAL ARTICLE

Repolarization Vector Magnitude Differentiates Kawasaki Disease from Normal Children

Daniel Cortez, M.D.,*† Sonali S. Patel, M.D., Ph.D.,*† Nandita Sharma, M.D.,‡
Bruce F. Landeck, M.D.,*† Anthony C. McCanta, M.D.,§ and Pei-Ni Jone, M.D.*†

From the *Children's Hospital Colorado, Aurora, CO; †University of Colorado School of Medicine, Aurora, CO;
‡Penn State Milton S. Hershey Medical Center, Hershey, PA; and §CHOC Children's, Orange, CA

Introduction: Kawasaki disease (KD) is the leading cause of acquired heart disease in children. The 12-lead electrocardiogram (ECG) changes in patients during the acute phase of KD include flattened T waves and prolonged corrected QT intervals (QTc). We set out to determine the 12-lead ECG and vectorcardiography predictors for identification of patients with KD and which of these predictors would be clinically useful for early identification of those with coronary artery anomalies (CAA).

Methods: A blinded, retrospective case-control study of patients with KD and age-matched controls was performed. Deep Q waves, QTc, spatial QRS-T angles, and T-wave vector magnitude (root mean square of the T wave, RMS-T) were assessed. Comparisons between groups were performed to test for significant differences.

Results: Fifty patients with KD (mean age 3.1 ± 3.1 years, 26% female) were compared to 50 previously healthy control patients (mean age 3.8 ± 2.9 years, 44% female). Of the KD patients, 32 (64%) were diagnosed as incomplete KD and 28 (56%) of them had CAA. When compared to the control group, KD patients had abnormal Q waves (72% vs 44% $P = 0.005$), shorter QTc values (395.1 ± 24.7 ms vs 410.4 ± 34.7 ms, $P = 0.013$), and lower RMS-T (0.42 ± 0.02 mV vs 0.63 ± 0.03 mV $P < 0.001$), respectively. Incomplete KD was also discriminated from controls by the same parameters. No differences were noted between KD patients with versus without CAA.

Conclusion: The RMS-T differentiates complete and incomplete KD from controls. KD patients with CAA were not differentiated from those without CAA.

Ann Noninvasive Electrocardiol 2016;21(5):493–499

pediatric-electrophysiology; electrocardiogram; echo

Kawasaki disease (KD) is a vasculitis that causes inflammation in multiple organ systems including the heart and coronary arteries. It is the leading cause of acquired heart disease in children.¹ Untreated children may develop coronary artery aneurysms or ectasia in 15–25% of KD cases.^{2,3} Early treatment in the acute phase aims at reducing inflammation in the coronary arterial wall and in those with coronary anomalies preventing myocardial ischemia or infarction.

The 12-lead electrocardiogram (ECG) changes in patients during the acute phase of KD include

flattened T waves and prolonged corrected QT intervals (QTc).⁴ A prolonged QTc, although sensitive, was not specific for KD patients with coronary artery anomalies (CAA) such as aneurysms.⁵ Deep Q waves (negative amplitude in various leads including I, AvL, II, AvF, and III) have been observed in KD patients with myocardial ischemia, while deep Q waves in lead V₆ have been associated with KD without myocardial ischemia.^{6,7} Furthermore, signal average ECG measurements have demonstrated evidence of QRS amplitude changes in patients with KD from illness

Address for correspondence: Daniel Cortez, M.D., 13123 East 16th Avenue, Box 100, Aurora, CO 80045. Tel: 303-718-6871; Fax: 720-777-7290; E-mail: Dr.danielcortez@gmail.com

No financial conflicts of interest to disclose.

onset through 1 year following diagnosis (including longer duration of low amplitude signals, terminal QRS root mean square voltage $<20 \mu\text{V}$, and filtered QRS duration $>114 \text{ ms}$).⁷

Vectorcardiography (VCG) is a method of recording the direction and magnitude of electrical forces generated by the heart by means of series of continuous vectors. The method most frequently utilized was developed by Dr. Ernest Frank and is chosen due to its ease of application and theoretical soundness.⁸ Recent advances have demonstrated that a spatial angle measure between ventricular depolarization and repolarization forces (the spatial QRS-T angle) can reliably be calculated based on the 12-lead ECG.⁹ This parameter has prognostic and diagnostic value in adults with myocardial ischemia and infarctions,¹⁰⁻¹³ however it has yet to be evaluated as a tool to identify those with KD or more importantly those with KD and CAA.

We hypothesize that three-dimensional T-wave amplitude quantification (RMS-T, via root mean square of X, Y, Z components) will differentiate patients with complete and incomplete KD from controls. We also hypothesize that the spatial QRS-T angle will differentiate KD patients with CAA from those KD patients without CAA.

METHODS

Patients

A blinded, retrospective case-control study of patients with KD and age-matched controls at the Children's Hospital of Colorado from 2008 to 2014 was performed. Cases were defined as complete or incomplete KD patients diagnosed by the American Heart Association criteria.¹⁴ Complete KD includes 5 days of fever (38.0°C) with four out of five of the following criteria: maculopapular rash, cervical lymphadenopathy of at least 1.5 cm in diameter, swelling of the hands/feet, conjunctival injection, and mucositis.¹⁴ Incomplete Kawasaki diagnosis includes 5 days of fever and two to three out of the above criteria along with laboratory criteria (C-reactive protein [CRP] $\geq 3 \text{ mg/dL}$ and/or erythrocyte sedimentation rate [ESR] $\geq 40 \text{ mm/h}$ and three or more supplemental laboratory criteria).¹⁴ All KD patients who were admitted had an ECG and an echocardiogram as part of standard of care. ECGs were obtained

on hospital admission day 1 prior to intravenous immunoglobulin or other intravenous immunomodulator administration. Only ECGs with flat baselines in leads I, II, or V_1 - V_6 , adequate for assessment of voltage parameters, were included. Poor quality ECGs with movement artifact were excluded. Standard echocardiograms were performed using the appropriate size transducers for pediatric patients and included assessment of proximal coronary arteries with Boston z-scoring applied. Controls were patients who presented to the cardiology clinic for evaluation of benign chest pain or benign murmurs without fever. Each control patient was determined to be normal by clinical examination, ECG, and echocardiogram. Patients with family history of ion-channelopathy on antiepileptic ion-channel altering medications were excluded as controls. Patients with echocardiographic evidence of myocardial dysfunction, dilated cardiomyopathy, or intracardiac shunting aside from a patent foramen ovale were also excluded from normal controls. The Institutional Review Board approved of this study and consents were waived.

ECG and Vector Evaluation

The first and third authors were blinded to the diagnosis of the patients during ECG read. ECGs (Phillips, NV, USA) were recorded at a speed of 25 mm/s with 10 mm/mV voltage reference for limb and precordial leads. At our institution these are all available in portable document format (PDF file). Deep Q waves were defined as Q waves with 5 mm or greater depth in the following leads: II, AvF, III, V_4 , V_5 , or V_6 .⁶ Deep Q waves were assessed. The QTc from Bazett's formula, spatial QRS-T angles, and T-wave vector magnitudes (RMS-T) were measured on all ECGs. Spatial QRS-T angles and principle T-wave component vector (RMS-T) are shown in Figures 1 and 2. The RMS-T was calculated as the square root of the sum of the squared T waves in leads V_6 , II, and one-half of the T-wave amplitude in V_2 ($\sqrt{TV_6^2 + TII^2 + (0.5 * TV_2)^2}$, Fig. 1) based on the T-wave magnitude as defined by the visually transformed Kors' quasi-orthogonal method.⁹ Spatial angles were calculated from the 12-lead ECGs based on a previously described visual application method.⁹

Figure 1. Calculation of the root mean square of the T wave (RMS-T).

Figure 2. A visual representation of spatial angles and vector magnitudes.

Coronary Artery Abnormality Classification

CAA were classified as mild, moderate, or severe dilation. Measurements of the coronary arteries were performed at the proximal right or left coronary origins, and Boston z-scores were applied using the body surface areas of the individual KD patients.¹⁵ Mild CAA dilation includes Boston z-score of 2.5–5, moderate dilation include z-score 5–10, and severe dilation as z-score greater than 10.

Statistical Analysis

Data were assessed for normality using Shapiro–Wilk testing. Normally distributed continuous data are presented as mean and standard deviation. Student's t-tests, chi-square, and analysis of variance were used to identify significant differences between groups. Receiver operating characteristic (ROC) curve analysis was performed to identify threshold values for VCG parameters associated with CAA. These limits were chosen with high negative predictive value especially for

patients with incomplete disease. Patients who test negative would likely have follow-up laboratory evaluation to assess whether they have incomplete KD. Odds ratios were calculated to estimate risk for parameters identified as significantly different by comparative analysis. Intraobserver and interobserver variability was estimated by intraclass correlation coefficients based on 20% of the population studied by the first and third authors (D.C. and N.S.) for the RMST. Data analysis was performed using the Statistical Analysis System (version 9.3, SAS Corporation, Cary, NC). A P value of < 0.05 was considered significant.

RESULTS

Cohort

One hundred patients fit our inclusion criteria. Fifty patients had the diagnosis of KD and 50 were matched control patients. Patient demographics are described in Table 1.

KD versus Controls

When patients with KD were compared to control subjects, significant differences were noted between the RMS-T values for the KD versus control patients (0.42 ± 0.02 mV vs 0.63 ± 0.03 mV $P < 0.001$) as well as between the presence of deep Q waves (72% in KD patients vs 44% in control patients, $P = 0.005$) and QTc values (395.1 ± 24.7 ms vs 410.4 ± 34.7 ms, $P = 0.013$). The RMS-T had the highest positive predictive value of 94%, while the QTc and deep Q waves had positive predictive values of 67% and 62%, respectively. None of the significantly differentiating parameters had high negative predictive values with deep Q waves, QTc, and RMS-T at 67%, 62%, and 60%, respectively. The spatial QRS-T angle did not significantly differentiate those with KD from control patients (Table 2). Please see Table 3 for odds ratios and ROC curve calculations. Heart rates for KD and controls were 106.8 ± 26.5 beats per minute (bpm) versus 103.7 ± 23.8 bpm without significant difference noted (P -value = 0.54).

Incomplete KD versus Controls

Thirty-two incomplete KD patients were identified among the KD group. Incomplete KD was similarly discriminated from control patients by

the RMS-T with a P value of 0.002. At an RMS-T cutoff value of 0.68 mV, sensitivity is 88% with specificity at 32% for identification of incomplete KD. At a cutoff of 0.30 mV, the sensitivity is only 31% but with a specificity of 98% and positive predictive value of 91% (Table 4, Fig. 3). Thus, at a cutoff of 0.30 mV an additional 10 patients would be classified as complete KD if RMS-T were added as additional criteria, and with only one false positive in the control group.

KD CAA versus KD Patients with No CAA

No significant differences existed between parameters tested in KD patients with CAA versus KD patients without CAA. Additionally, group differences were not identified in terms of degree of dilation of the coronary arteries (Table 5).

Multivariate Analysis

When controlled for age and gender, the RMS-T remained the only independent predictor of KD (P -value < 0.001) with an adjusted odds ratio of 13.5 (95% confidence interval 2.7 to 67.5).

Intraobserver and Interobserver Variability

Intraclass correlation coefficients for intra- and interobserver variability for the RMS-T were 0.975 and 0.965, respectively.

DISCUSSION

KD versus Controls

Our study demonstrated that KD patients can be distinguished from controls by the RMS-T. Incomplete KD patients can also be distinguished from controls using the same parameter. Similar to prior results, our study demonstrated that the presence of deep Q waves and the QTc does differentiate control patients from those with KD but with less diagnostic accuracy than the RMS-T.^{4,6,7} The QTc was calculated by the Bazett's formula, which has recently been shown to be an appropriate correction in children and infants.¹⁶

The findings of lower RMS-T in patients with KD versus control patients appear to correlate with repolarization abnormalities found in KD patients reported previously,⁴ but suggest that T-wave vector magnitude voltage has more

Table 1. Patient Demographics

Patient Demographics	Kawasaki Disease (N = 50)	Controls (N = 50)	P Value
Age (years)	3.1 ± 3.1	3.8 ± 2.9	0.861
Female gender	13 (26%)	22 (44%)	0.059
Incomplete Kawasaki disease (%)	32 (64%)	NA	NA
Coronary artery abnormalities (%)	28 (56%)	0 (0%)	<0.001

Table 2. Vectorcardiographic and Electrocardiographic Parameters Based on Presence of Kawasaki Disease Including Deep Q Waves, Corrected QT Interval (QTc), Spatial QRS-T Angles, and T-Wave Vector Magnitude (RMS-T)

	Kawasaki Disease (N = 50)	Controls (N = 50)	P Value
Deep Q waves	36.0 (72.0%)	22.0 (44.0%)	0.005
QTc (ms)	395.1 ± 24.7	410.4 ± 34.7	0.013
Spatial QRS-T angle (deg)	35.7 ± 26.1	29.9 ± 19.0	0.200
RMS-T (mV)	0.42 ± 0.02	0.63 ± 0.03	<0.001

Table 3. Receiver Operating Characteristic Curve Analysis Including Deep Q Waves, Corrected QT Interval (QTc), and the Root Mean Square of the T Wave (RMS-T) for KD versus Control Patients

	Sensitivity	Specificity	AU ROC (95% Confidence Interval)	Odds Ratio (95% Confidence Interval)
QTc (ms)	0.56	0.72	0.65 (0.56 to 0.74)	3.27 (1.42 to 7.52)
RMS-T	0.34	0.98	0.74 (0.66 to 0.82)	25.2 (3.2 to 199.0)
Deep Q waves	0.72	0.56	N/A	3.27 (1.42 to 7.52)

AUC = area under curve.

Table 4. Incomplete KD (N = 32) versus Control Patients (N = 50) with Specific Cutoff Values for Identification of Disease Based on the T-Wave Vector Component Magnitude (RMS-T) and Their Associated Sensitivities and Specificities

RMS-T (mV)	Sensitivity (%)	Specificity (%)
0.68	88.0	32.0
0.58	75.0	56.0
0.48	66.0	74.0
0.40	55.7	87.0
0.30	31.0	98.0

diagnostic accuracy than the length of the QTc. The RMS-T quantifies the flattening of the T waves in a three-dimensional space (which includes multiple leads) and thus, may demonstrate a change in the dispersion of repolarization. In KD, during the acute inflammatory phase, T-wave flattening and ST changes may be apparent prior to echocardiographic changes.⁴ Much like changes in another acute inflammatory heart disease, i.e.,

myocarditis, the more diffuse the myocardial inflammation, the more T-wave inversions and overall magnitude changes are present.¹⁷ KD, being a diffusely infiltrating inflammatory disease, likely affects the myocardium in a similar manner; thus, with change in direction of some of the T waves, a greater dispersion of repolarization exists. The RMS-T may be helpful in identifying incomplete KD patients when the diagnosis is unclear. This may prevent delay in treatment of KD and the development of CAA.^{2,3}

A low RMS-T gives a high positive predictive value for complete or incomplete KD; however, the negative predictive values for all parameters tested were not high enough to be clinically helpful. If someone is suspecting incomplete KD, a low RMS-T calculation (if independently reproduced in larger cohorts) may help quickly confirm this suspicion and help the patient receive treatment quickly. The importance of this parameter is that at the cutoff chosen there is a lot false positive value (specificity of 98% yielding 2% false positive value), which may help to improve earlier diagnosis

Figure 3. Incomplete Kawasaki disease (KD) versus controls patients RMS-T (dmV).

Table 5. Electrocardiographic and Vectorcardiographic Parameters Based on the Presence of Coronary Artery Abnormalities Including Deep Q Waves, Corrected QT Interval (QTc), Spatial QRS-T Angles, and the Root Mean Square of the T Wave (RMS-T)

	Coronary Anomalies (N = 27)	No Coronary Anomalies (N = 23)	P Value
Deep Q waves (%)	19.0 (70.4%)	16.0 (69.6%)	0.951
QTc (ms)	400.8 ± 19.8	390.2 ± 27.7	0.122
Spatial QRS-T angle (deg)	36.8 ± 28.2	35.4 ± 23.9	0.935
RMS-T (mV)	0.37 ± 0.22	0.41 ± 0.17	0.535

of KD if RMS-T is greater than 0.30 mV. With a test such as this, it is important to have a low false positive value as to avoid overdiagnosis or overtreatment of KD if this parameter were to be implemented. If the RMS-T is high, then continuing with further diagnostic testing to confirm full incomplete criteria is met would be warranted prior to treatment. Although outside the scope of this study, it would be interesting to correlate inflammatory markers to RMS-T in future studies to see what correlations exist, as inflammation, much like myocardial disorganization, causes some degree of dispersion of repolarization, but unlike myocardial disorganization, does not seem to affect the three-dimensional angle between the depolarization and repolarization peak vectors.¹⁸

KD CAA versus KD Patients with No CAA

The spatial QRS-T angle did not differentiate KD patient with CAA compared to those without CAA. The presence of coronary aneurysms does not necessarily indicate myocardial ischemia. The spatial QRS-T angle identifies those with ischemic heart

disease and myocardial infarctions due to change in angle of the vectors of depolarization and repolarization, as injured tissue, even with only partial thickness necrosis does not conduct electricity as well and thus the depolarization and repolarization vectors must change direction around those areas to continue down- and upstream.^{10–12,18} Only some patients with CAA who have thrombotic occlusions have ischemia,² thus likely only those patients would have evidence of change in direction of depolarization or repolarization vectors, and thus a larger spatial QRS-T angle. Identification of ischemic heart disease was not within the goals of this study, and thus will have to be explored at a later time. A significant difference in deep Q waves was not observed in those with CAA compared to those without CAA. Q wave abnormalities have been identified in those with and without ischemia, but this was not found in our KD patients with CAA.^{6,7}

Limitations

The main limitation of this study is its retrospective nature and thus, the parameters tested

have not been applied prospectively. Orthogonal lead systems were not available for analysis, and thus all methods were applied using visual application methods on PDF file-based imaging of the recordings, thus some degree of error (although small based on the spatial QRS-T angle and its reproducibility) exists.⁹

CONCLUSION

Changes in repolarization, specifically the T-wave vector component, help to differentiate KD from control patients and confer a higher risk of KD than any other component tested. Incomplete KD is similarly discriminated from control patients with potentially clinically useful discriminatory ability, so the incomplete KD patients can be identified earlier for treatment to prevent coronary artery dilations or aneurysms. The ECG, based on the parameters tested, does not have diagnostic utility in identification of CAA in patients with KD. Larger prospective studies are needed to validate these results.

REFERENCES

1. Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children [in Japanese]. *Arerugi* 1967;16:178.
2. Kato H, Sugimura T, Akagi T, et al. Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. *Circulation* 1996;94:1379-1385.
3. Dajani AS, Taubert KA, Gerber MA, et al. Diagnosis and therapy of Kawasaki disease in children. *Circulation* 1993;87:1776-1780.
4. Ichida F, Fatica NS, O'Loughlin JE, et al. Correlation of electrocardiographic and echocardiographic changes in Kawasaki syndrome. *Am Heart J* 1988;116:812-819.
5. Hiew TM, Cheng HK. ECG abnormalities in Kawasaki disease and their value in predicting coronary artery aneurysms. *Singapore Med J* 1992;33:262-267.
6. Nakanishi T, Takao A, Kondoh C, et al. ECG findings after myocardial infarction in children with Kawasaki disease. *Am Heart J* 1988;116:1028-1033.
7. Crystal MA, Syan SK, Yeung RSM, et al. Echocardiographic and electrocardiographic trends in children with acute Kawasaki disease. *Can J Cardiol* 2008;24:776-780.
8. Frank E. An accurate, clinically practical system for spatial vectorcardiography. *Circulation* 1956;13:737-749.
9. Cortez D, Sharma N, Devers C, et al. Visual transform applications for estimating the spatial QRS-T angle from the conventional 12-lead ECG: Kors is still most frank. *J Electrocardiol* 2014;47:12-19.
10. Triola B, Olson MB, Reis SE, et al. Electrocardiographic predictors of cardiovascular outcome in women: The National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. *J Am Coll Cardiol* 2005;46:51-56.
11. de Torbal A, Kors JA, van Herpen G, et al. The electrical T-axis and the spatial QRS-T angle are independent predictors of long-term mortality in patients admitted with acute ischemic chest pain. *Cardiology* 2004;101:199-207.
12. Rautaharju PM, Ge S, Nelson JC, et al. Comparison of mortality risk for electrocardiographic abnormalities in men and women with and without coronary heart disease (from the cardiovascular health study). *Am J Cardiol* 2006;97:309-315.
13. Yamazaki T, Froelicher VF, Myers J, et al. Spatial QRS-T angle predicts cardiac death in a clinical population. *Heart Rhythm* 2005;2:73-78.
14. Council on Cardiovascular Disease in the Young; Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease; American Heart Association. Diagnostic guidelines for Kawasaki disease. *Circulation* 2001;103:335-336.
15. McCrindle BW, Li JS, Minich LL, et al. Coronary artery involvement in children with Kawasaki disease, risk factors from analysis of serial normalized measurements. *Circulation* 2007;116:174-179.
16. Phan DQ, Silka MJ, Lan YT, et al. Comparison of formulas for calculation of the corrected QT interval in infants and children. *J Pediatr* 2015;166:960-964.
17. Nucifora G, Miani D, Di Chiari A, et al. Infarct-like acute myocarditis: Relation between electrocardiographic findings and myocardial damage as assessed by cardiac magnetic resonance imaging. *Clin Cardiol* 2013;36:146-152.
18. Cortez D, Sharma N, Cavanaugh J, et al. The spatial QRS-T angle outperforms the Italian and Seattle ECG-based criteria for detection of hypertrophic cardiomyopathy in pediatric patients. *J Electrocardiol* 2015;48:826-833.