ORIGINAL ARTICLE

Atrioventricular depolarization differences identify coronary artery anomalies in Kawasaki disease

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Background: Kawasaki disease (KD) is the leading cause of acquired heart disease in children. Signal average electrocardiogram changes in patients during the acute phase of KD with coronary artery anomalies (CAA) include depolarization changes. We set out to determine if 12-lead-derived atrioventricular depolarization differences can identify CAA in patients with KD.

Methods: A blinded, retrospective case-control study of patients with KD was performed. Deep Q waves, corrected QT-intervals (QTc), spatial QRS-T angles, T-wave vector magnitudes (RMS-T), and a novel parameter for assessment of atrioventricular depolarization difference (the spatial PR angle) and a two dimensional PR angle were assessed. Comparisons between groups were performed to test for significant differences.

Results: One hundred one patients with KD were evaluated, with 68 having CAA (67.3%, mean age 3.6 ± 3.0 years, 82.6% male), and 32 without CAA (31.7%, mean age 2.7 ± 3.2 years, 70.4% male). The spatial PR angle significantly discriminated KD patients with CAA from those without, $59.7^\circ \pm 31.1^\circ$ versus $41.6^\circ \pm 11.5^\circ$ ($p < .001$). A spatial PR angle cutoff value of 56.9° gave positive/negative predictive values and odds ratios of 93.8%, 43.5%, and 11.5% (95% confidence interval (CI) 2.6–52.2). The two dimensional PR angle either below 7° or above 92° gave positive/negative predictive values and odds ratios of 100.0%, 38.8%, and 21.1% (95% CI 1.2–362.8). No other parameters significantly differentiated the groups.

Conclusion: Atrioventricular depolarization differences, measured by the spatial or two dimensional PR angle differentiate KD patients with CAA versus those without.

KEYWORDS

coronary artery anomalies, Kawasaki, PR angle, vectorcardiography

Kawasaki disease (KD) is a vasculitis of unknown etiology that causes systemic inflammation including the heart and coronary arteries. It is the leading cause of acquired heart disease in children (Kawasaki, 1967; Newburger, Takahashi, & Burns, 2016). If children remain untreated, they may develop coronary artery aneurysms or ectasia (defined as coronary artery anomalies, CAA) in 20%–25% of KD cases (Dajani et al., 1993; Kato et al., 1996). Early treatment in those with coronary anomalies aims to reduce inflammation in the coronary arterial wall and prevent myocardial ischemia or infarction. Additional therapy with infliximab has been shown to have more rapid resolution

of fever and inflammatory markers, shorter hospital stay, and lower cost of stay (Tremoulet et al., 2014). Early, cost-effective identification of KD patients with CAA is paramount in improving long-term outcomes (Dajani et al., 1993; Kato et al., 1996).

Quantifiable T wave changes (T wave vector magnitudes) were also recently shown to differentiate KD from control patients, including incomplete KD from control patients, but along with the spatial QRS-T angle (a three dimensional vectorcardiographic angle measured utilizing the method by Dr. Ernest Frank which can identify myocardial ischemia and predict myocardial infarctions), and the QTc were not able to

differentiate KD with CAA from those without CAA (Cortez, Sharma, Devers, Devers, & Schlegel, 2014; Cortez et al., 2016; Frank, 1956; Hiew & Cheng, 1992; Ichida et al., 1988; Rautaharju et al., 2006; de Torbal et al., 2004; Triola et al., 2005). Deep Q waves, however, have been observed in KD patients with (Nakanishi et al., 1988) and without myocardial ischemia (Crystal, Syan, Yeung, Dipchand, & McCrindle, 2008).

A spatial angle between ventricular depolarization forces compared to atrial depolarization forces (a PR angle), however, has yet to be assessed in the literature, and may be another way to assess inflammatory-induced ventricular depolarization differences, like those seen in KD patients with CAAs.

The main objective of this study was to utilize a novel three dimensional atrial-ventricular depolarization angle (please see Figs. 1 and 2) to attempt to identify KD patients with CAA versus those without

CAA. We will also test a two-dimensional PR angle (reported QRS axis minus P axis, Fig. 2) in the same manner.

1 | METHODS

1.1 | Patients

A blinded, retrospective case-control study of patients with KD at the Children's Hospital of Colorado from 2008–2015 was performed. Cases were defined as complete or incomplete KD patients diagnosed by American Heart Association criteria (Council on Cardiovascular Disease in the Young; Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease; American Heart Association, 2001). Complete Kawasaki disease includes 5 days of fever (38.0°C) with four 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 (Council on Cardiovascular Disease in the Young et al., 2001). Incomplete Kawasaki diagnosis includes 5 days of fever and 2–3 out of the above criteria along with laboratory criteria (CRP ≥ 3.0 mg/dl and/or ESR ≥ 40 mm/hr and 3 or more supplemental laboratory criteria) (Council on Cardiovascular Disease in the Young et al., 2001). All KD patients who were admitted had an electrocardiogram (ECG) and an echocardiogram as part of standard of care. Only ECGs with flat baselines in leads I, II, or V₁–V₆, adequate for assessment of voltage parameters, were included. Only ECGs taken prior to administration of standard Kawasaki disease treatment (IVIg or IVIG/infliximab) were used. ECGs taken after treatment were not used as the aim of the study was to identify KD with CAA to possibly guide treatment when echocardiograms are limited or unavailable. 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. Patients with family history of ion-channelopathy or on antiepileptic ion-channel altering medications were excluded. Patients with echocardiographic

FIGURE 1 A visual representation of spatial angles and vector magnitudes

FIGURE 2 Calculation of the spatial PR angle and two dimensional angle
P AXIS: 60°, QRS AXIS: 30°, TWO DIMENSIONAL PR ANGLE = QRS – P AXES = 30–6 = –36°.
 RMS P wave = $\sqrt{[x^2 + y^2 + z^2]} = \sqrt{[0.5^2 + 1.5^2 + 9(-0.5 \times 0.5)^2]} = 1.6$ mm (dmV)
 RMS QRS wave = $\sqrt{[x^2 + y^2 + z^2]} = \sqrt{[11^2 + 6.5^2 + (-0.5 \times 12)^2]} = 14.1$ mm (dmV).
 Spatial peaks PR angle = $\cos^{-1}[(Px \times QRSx + Py \times QRSy + Pz \times QRSz)/RMSP \times RMSQRS] = 80.2^\circ$.

evidence of myocardial dysfunction, dilated cardiomyopathy, or intracardiac shunting aside from a patent foramen ovale were also excluded. The institutional review board approved this study and consents were waived.

1.2 | ECG and vector evaluation

The 1st and 2nd authors were blinded to the diagnosis of the patients during ECG read. ECGs (Philips, Andover, MA, 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). The corrected QT-intervals (QTc) from Fredericia's formula, spatial QRS-T angles, and T-wave vector magnitudes (RMS-T) were measured on all ECGs. Deep Q waves were defined as Q waves with 5 mm or greater depth in the following leads: II, AvF, III, V₄, V₅, or V₆ (Nakanishi et al., 1988). Spatial QRS-T and PR angles as well as principle T-wave component vector (RMS-T) are shown in Fig. 1. The RMS-T was calculated as the square root of the sum of the squared T waves in leads V₆, II and one half of the T-wave amplitude in V₂ ($\sqrt{TV_6^2 + T_{II}^2 + (0.5 \times TV_2)^2}$) based on the T-wave magnitude as defined by the visually transformed Kors' Quasi-orthogonal method (Cortez et al., 2014). Spatial QRS-T and PR angles as well as principle T-wave component vector (RMS-T) are shown in Fig. 1. The RMS-T was calculated as the square root of the sum of the squared T waves in leads V₆, II and one half of the T-wave amplitude in V₂ ($\sqrt{TV_6^2 + T_{II}^2 + (0.5 \times TV_2)^2}$) based on the T-wave magnitude as defined by the visually transformed Kors' Quasi-orthogonal method (Cortez et al., 2014, 2016). Spatial angles were calculated from 12-lead ECG's based on a previously described visual application method (de Torbal et al., 2004). Spatial PR angles (SPR angles) are shown in Figs 1 and 2. Spatial QRS-T angles were calculated from 12-lead ECG's based on a previously described visual application method (Cortez et al., 2014). The spatial PR angle was calculated by the Kors' Quasi-orthogonal method applied to P and QRS waves. Please see Fig. 2 for an example of this calculation. This method was chosen based on an unpublished study by the first author which compared nine different methods including Kors' regression-related, quasi-orthogonal, inverse dower, as well as six other methods to assess best visual application method as compared to Frank lead measured spatial PR angles, which identified the Kors' quasi-orthogonal method with the tightest Bland Altman limits of agreement and highest Pearson correlation coefficient. Two dimensional PR angles were calculated based on the reported QRS-axis minus the reported P axis (bipolar QRS axis minus bipolar P axis, Fig. 2).

1.3 | Coronary artery abnormality classification

Coronary artery anomalies 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 (Council on Cardiovascular Disease in the Young et al., 2001).

Mild CAA dilation include Boston z-score of 2.5–5, moderate dilation include z-score 5–10, and severe dilation as z-score > 10.

1.4 | Statistical analysis

Data were assessed for normality using Shapiro–Wilk testing. Normally distributed continuous data are presented as mean and standard deviation. Student 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. 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 second authors (D.C. and N.S.) for spatial PR angles. Data analysis was performed using the Statistical Analysis System (version 9.3, SAS Corporation, Cary, NC, USA). A *p*-value of <.05 was considered significant.

2 | RESULTS

2.1 | Cohort

One hundred and one patients with the diagnosis of KD with ECG's prior to IVIG or Infliximab were identified (please see Table 1 for demographics). No significant differences were found between those with incomplete versus complete KD patients or between different degrees of coronary dilation (mild, moderate, severe).

2.2 | KD CAA versus KD patients without CAA

The spatial PR angle and two dimensional PR angle both significantly differentiated KD patients with CAA and those without CAA (*p*-values of <.001 and .006, respectively, Table 1). The area under the ROC curve for the spatial PR angle was 0.75 (95% confidence interval 0.64–0.87). A spatial PR angle cutoff value of 57.9° was associated with a sensitivity of 44.1%, specificity of 93.9%, positive predictive value of 93.8%, and negative predictive value of 43.5% (AUC = 0.75, Table 2) and odds ratio of 11.5 (95% CI 2.6–52.2, Table 2); whereas, at a cutoff of 1 standard deviation above the mean spatial PR angle for controls (53.1°) yielded a sensitivity, specificity, positive, and negative predictive values of 48.5%, 87.9%, 89.2%, and 45.3% and odds ratio of 6.8 (95% CI 2.2–21.6). A two dimensional PR angle with a cutoff of <7° or >92° was associated with a sensitivity of 23.5%, specificity of 100.0%, positive predictive value of 100.0%, negative predictive value of 38.8%, and odds ratio of 21.1 (95% CI 1.2–362.8, Table 2). No significant differences were not noted for deep Q waves, QTc, spatial QRS-T angle, or RMS-T between those KD patients with CAA compared to those without CAA. In addition, group differences were not identified in terms of degree of dilation of the coronary arteries, nor between patient with persistent fever >24 hours after first intravenous medical treatment versus not resistance to initial treatment were noted. Interestingly, however, only three of the 16 (18.8%) with mild single

	KD no CAA (n = 32)	KD CAA (n = 68)	p Value
Age (years)	2.7 ± 3.2	3.6 ± 3.0	.278
Age < 1 year (%)	3 (9.4%)	24 (35.3%)	.007
Sex (male %)	27.0 (84.4%)	56.0 (82.4%)	1.000
Caucasian (%)	28 (87.5%)	51 (75.0%)	.193
Black (%)	1 (3.1%)	2 (2.9%)	1.000
Hispanic (%)	4 (12.5%)	12 (17.7%)	1.000
Asian (%)	1 (3.1%)	3 (4.4%)	1.000
Incomplete KD (%)	22 (68.8%)	50 (73.5%)	.797
Resistant (%)	3 (9.1%)	17 (25.0%)	.106
Deep Q waves (%)	13 (39.4%)	19 (27.9%)	.299
Corrected QT interval (ms)	393.6 ± 16.9	387.3 ± 26.8	.218
Spatial QRS-T angle (°)	36.8 ± 28.2	35.4 ± 23.9	.935
RMS-T (mV)	3.7 ± 2.2	4.1 ± 1.7	.535
2D PR angle <7° or >92°	0 (0.0%)	16 (23.5%)	.006
Spatial PR angle (°)	41.6 ± 11.5	59.7 ± 31.1	<.001

Bold values indicate significant *p*-value <.05.

TABLE 1 Demographics, electrocardiographic, and vectorcardiographic parameters based on presence of coronary artery abnormalities (CAA) including age (years), sex (male percentage), deep Q waves, corrected QT interval (QTc), spatial QRS-T, root mean square of the T wave (RMS-T, millivolts), two-dimensional PR angle at cutoff of <7° or >92°, and spatial PR angles (degrees) with associated *p*-values

TABLE 2 Coronary artery anomaly: sensitivity, specificity, area under the receiver operating characteristic curve (AU ROC) with 95% confidence interval (95% CI), positive predictive value (PPV%), negative predictive value (NPV%), and odds ratio at cutoff values for Spatial PR angle of 56.9° and for two dimensional PR angle (bipolar QRS angle—P angle) either <7° or >92°

	PPV (%)	NPV (%)	AU ROC (95% CI)	Odds ratio (95% CI)
Spatial PR angle (°)	93.8	43.5.0	0.75 (0.64–0.87)	11.5 (2.6–52.2)
2D PR angle <7° or >92°	100.0	38.8	N/A	21.1 (1.2–362.8)

vessel CAA were identified by the spatial PR angle above 57.9° or by a two dimensional PR angle of <7 or above 92°, while 27 of the remaining 52 patients with multivessel or moderate to severe CAA (51.9%) were identified by a spatial PR angle of 57.9°. Thirteen of the remaining 52 patients with multivessel or moderate to severe CAA (25.0%) were identified by a two dimensional PR angle <7° or above 92°.

2.3 | Development of CAA within 1 month and with regression of CAA at 1 month

The spatial PR angle for the four patients who developed CAA within 1 month of follow-up gave a median value of 58.3° (interquartile range 49.3°–61.6°). Three of the four patients had a PR angle above 57.9° and three had a two dimensional PR angle between 7° and 92°. There were no significant differences noted in the two dimensional of spatial PR angles between those who had regression of their CAA versus those without regression of their CAA at 1 month after initial presentation.

2.4 | Regression analysis two-dimensional PR angle versus spatial (three dimensional) PR angle

R-value for two-dimensional PR angle versus spatial PR angle was 0.757. Given this correlation, multivariate analysis was not performed for fear of collinearity between the two variables and given no other variables were deemed significant discriminators.

2.5 | Correlation of measures with maximum coronary Boston z-score

The *R*-value when the spatial PR angle was compared to maximum coronary Boston z-score was 0.415, where as the *R*-value for the two dimensional PR angle compared to maximum coronary Boston z-score 0.450.

2.6 | Correlation coefficients

Intra- and interclass correlation coefficients for spatial PR angles were 0.917 and 0.967, respectively.

3 | DISCUSSION

This study demonstrates that coronary anomalies during the acute phase of KD can be identified by an ECG with high positive predictive value due to angular difference between the ventricular depolarization vector and the atrial depolarization vector, whether in the frontal plane or in the spatial plane.

Similar to previous findings in those with coronary artery abnormalities which demonstrate changes in depolarization, our finding of depolarization differences between the atrial and ventricular maximum vectors (spatial and two dimensional PR angles) also suggests

differences in ventricular depolarization in KD patient with CAA compared to those without CAA (Ogawa et al., 1996). Although the mechanism is not entirely clear, if demonstrated prospectively, this may clinically help to identify CAA quickly, especially in communities where echocardiography is not so readily accessible. Also if reproducible in larger cohorts, this parameter may help patients with CAA obtain more timely treatment, as treatment differences exist for KD patients with CAA versus those without CAA (McCandless et al., 2013). The spatial PR angle can be calculated utilizing the equations in Fig. 2, and the two dimensional PR angle is even more simply calculated, based on the reported QRS-axis minus the reported P axis (also Fig. 2). This is more cost-effective than assessing strain by echocardiogram, which can differentiate those KD patients with CAA from those without CAA (Beladan et al., 2014).

As global longitudinal strain has been demonstrated to differentiate those KD patients with versus those without CAA, and since it correlates with left ventricular voltage, it is not unreasonable to expect other calculated ventricular depolarization changes in KD, such as the spatial PR angle, to discriminate between those with versus those without CAA (Beladan et al., 2014; Yutsni et al., 1981). Further investigation into the exact mechanism of atrial/ventricular vector separation in those with CAA warrants further investigation; however, may be related to worse inflammation at the myocardial level. More biopsy confirmed myocardial inflammation in the acute stage is found in those with coronary anomalies and thus the ventricle (which has greater coronary artery distribution than the atria) may have more inflammation proportionally and thus further depolarization direction change (Cortez et al., 2015; Yonesaki et al., 2010). More investigation into this mechanism is needed, however.

As with our previous study with half the number of KD patients, 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 up-stream (Rautaharju et al., 2006; de Torbal et al., 2004; Triola et al., 2005; 23). Only some patients with CAA who have thrombotic occlusions have ischemia, thus likely only those patients would have evidence of change in direction of depolarization compared to repolarization vectors, and thus a larger spatial QRS-T angle (Kato et al., 1996). Identification of ischemic heart disease was not within the goals of this study as not enough patients with detectable thromboses were assessed to provide sufficient power to study differences. However, subtle ventricular depolarization differences, such as those which may be detected by strain analysis when compared to a fixed atrial depolarization vector (since the atrial is typically less affected proportionally by coronary blood flow changes), may be detected by the spatial PR angle (Beladan et al., 2014; Yutsni et al., 1981).

A significant difference in deep Q waves was not observed in those with CAA compared to those without. Q wave abnormalities have been identified in those with as well as those without ischemia, thus it is not surprising that it does not clearly differentiate KD patients with versus those without CAA (Crystal et al., 2008; Nakanishi et al., 1988). The QTc did not differentiate between KD with CAA versus KD without CAA.

4 | LIMITATIONS

The main limitation of this study is its retrospective nature and thus, the parameters tested have not been applied prospectively. Furthermore, this altered the proportion of KD patients with CAA versus what would be in true accordance with a population prevalence. This showed us that our own institution orders echocardiograms first then ECG's. Therefore, our institution's bias for pre-treatment ECG's mainly in CAA presence was apparent. Otherwise, orthogonal lead systems were not available for analysis, and thus all methods were applied using visual application methods, thus some degree of error (although small and reproducible) exists (Cortez et al., 2016; Triola et al., 2005). Furthermore, this was a hypothesis generating study and is important to note as a limitation.

5 | CONCLUSION

Kawasaki patients with CAA have some atrio-ventricular depolarization differences compared to those without coronary changes with high positive predictive values whether by two dimensional or spatial PR angles. Q wave changes and the QTc do not discriminate between those with versus those without CAA. Larger prospective studies are needed to validate these results.

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