Echocardiographic and electrocardiographic trends in children with acute Kawasaki disease

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BACKGROUND: Kawasaki disease (KD), while primarily an acute, self-limited, multisystem vasculitis, is more appropriately described as a pancarditis, from a cardiac perspective. Many patients are noted to have ventricular dilation on initial echocardiography; however, functional and structural measurements may remain within the normal range.

OBJECTIVE: The authors sought to determine echocardiographic and electrocardiographic trends after acute KD.

METHODS: Clinical data were reviewed on all patients presenting with acute KD to the Hospital for Sick Children (Toronto, Ontario). Patients with at least three electrocardiograms and echocardiograms over the first year post-KD were eligible. Mixed linear regression analysis for repeated measures was used to determine trends over time and associated factors.

RESULTS: One hundred seventy-six eligible patients were reviewed. Mean initial coronary artery diameter Z-scores were increased, with 4% having aneurysms. The mean ($\pm$ SD) initial Z-score of ejection fraction was 0.40 ± 0.84 ($P < 0.001$ versus normal) and left ventricular end-diastolic dimension (LVED) was 0.97 ± 0.98 ($P < 0.001$ versus normal). The initial mean QT dispersion was 54 ± 23 ms ($P < 0.001$ versus normal). Mixed linear regression analysis for repeated measures demonstrated that the LVED Z-score decreased significantly over time, and a greater Z-score was independently associated with a greater initial LVED Z-score. Increased QT dispersion was only related to higher initial dispersion, with no trend over time.

CONCLUSIONS: While systolic ventricular dysfunction may not be evident, subclinical myocardial involvement may be indicated by subtle ventricular dilation and repolarization abnormalities.

Key Words: Coronary arteries; Echocardiography; Electrocardiography; Kawasaki disease

Tendances échocardiographiques et électrocardiographiques chez les enfants atteints de maladie de Kawasaki

HISTORIQUE : La maladie de Kawasaki (MK), tout en étant principalement une vascularite spontanément résolutive plurisystémique, serait plus adéquatement décrite comme une pancardite d'un point de vue cardiologique. De nombreux patients présentent une dilatation ventriculaire à l'échocardiographie initiale, mais leurs paramètres fonctionnels et structurels peuvent rester à l'intérieur des limites de la normale.

OBJECTIF : Les auteurs ont tenté de dégager les tendances échocardiographiques et électrocardiographiques observables à la suite d'une MK aiguë.

MÉTHODES : Les données cliniques ont été passées en revue pour tous les patients qui se sont présentés avec une MK aiguë au *Hospital for Sick Children* (de Toronto en Ontario). Les patients pour lesquels on disposait d'au moins trois électrocardiogrammes et échocardiogrammes pour la première année suivant la MK étaient admissibles. Les auteurs ont dégagé les tendances chronologiques et les facteurs associés en appliquant une analyse de régression linéaire mixte aux paramètres enregistrés successivement.

RÉSULTATS : Les auteurs ont analysé 176 cas jugés admissibles. Les scores Z pour le diamètre coronarien initial moyen étaient augmentés, 4 % présentant des anévrismes. Le score Z initial moyen ($\pm$ ÉT) de la fraction d'éjection était de $0,40 \pm 0,84$ ($P < 0,001$ vs normale) et la dimension télédiastolique du ventricule gauche (DTDVG) était de $0,97 \pm 0,98$ ($P < 0,001$ vs normale). La dispersion initiale moyenne du QT était de 54 ± 23 ms ($P < 0,001$ vs normale). L'analyse de régression linéaire mixte pour les mesures répétées a révélé que le score Z de la DTDVG avait significativement diminué avec le temps et un score Z plus élevé était associé de manière indépendante à un score Z de la DTDVG initiale plus élevé. L'augmentation de la dispersion QT n'a été associée qu'à une dispersion initiale plus élevée, sans tendance chronologique nette.

CONCLUSION : Si la dysfonction ventriculaire systolique n'est pas toujours perceptible, l'atteinte myocardique subclinique se manifeste parfois par une dilatation ventriculaire et des anomalies subtiles de la repolarisation.

Kawasaki disease (KD), while primarily an acute, self-limited, multisystem vasculitis, is more appropriately described as a pancarditis, from a cardiac perspective (1-4). The coronary arteries remain the most prominently affected, although the majority have dilation only. Ventricular dysfunction and arrhythmias also occur, and may do so independent of coronary artery involvement (5,6). This may be indicated by echocardiographic (echo) abnormalities in ventricular dimensions and function, and electrocardiographic (ECG) abnormalities in ventricular forces and repolarization. Many patients are believed to have ventricular dilation on initial echo; however, functional and structural measurements may remain within the normal range. In addition, the relationship between possible markers of myocardial inflammation and the degree of coronary artery abnormalities has not been well characterized. Therefore, we sought to determine the relationship between echo and ECG trends after acute KD.

METHODS

Study population

All patients diagnosed and admitted with acute KD (typical and atypical) to the Hospital for Sick Children, Toronto, Ontario, over a three-year time period were included in the present study. Ethics approval was obtained from the Hospital for Sick Children's institutional research ethics board. The clinical data reviewed included symptomatology, ECG and echo studies. To meet eligibility criteria, patients had to have available echos for each of three time periods, including the initial (acute), the six- to eight-week and the one-year period post-KD. For eligible patients, all interim echos were also included.

Measurements

The medical records of all patients were reviewed to obtain data regarding demographics, clinical features of KD and management.

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Serial ECG and echo measurements were recorded. Selected ECG measurements were made from paper recordings using hand calipers by a single trained observer. Measurements believed to represent the status of the left ventricle were chosen, and included QT interval and the height of the R wave in lead V6, depth of the S wave in lead V1 and depth of the Q wave in lead V6. The end of the T wave was defined as the point of return to baseline, and in the rare presence of a U wave, the U wave was not included and the T wave was extrapolated to baseline. QT dispersion was calculated as the difference between the minimum and maximum QT intervals for any of the 12 leads. Echo data were obtained from the final reports, and all measurements were obtained in accordance with common standard practice in the laboratory, which did not change during the study period. Echo data abstracted from the reports included the coronary artery diameters (measured as the internal diameter of the vessel from internal edge to internal edge) and cardiac chamber dimensions (measured from leading edge to leading edge of the endocardium by M-mode in the parasternal long-axis view), functional parameters and all general descriptors.

Data analysis

Patient characteristics are described using frequencies, medians with ranges and mean $\pm$ SD. All echo measurements were normalized for body surface area from height and weight as Z-scores based on published data from normal, nonfebrile control subjects (7,8). Coronary artery involvement was noted from both subjective comments from the reports (dilation was defined as the presence of increased dimensions in the absence of aneurysms), and also from coronary artery Z-scores exceeding 2. QT dispersion was calculated from the 12-lead ECG as described in other studies and analyzed as Z-scores, using published normal mean $\pm$ SD (9-11). Information was not available for normalization of ECG voltage criteria for Q, R and S waves, so actual measurements were analyzed. These were taken from computer-generated μ V measurements and can be divided by 1000 to be viewed as mV. A mixed linear regression analysis for repeated measures was used to determine trends over time and factors associated with serial ECG and echo measurements, as well as their interactions and correlations. All analyses were performed using SAS statistical software version 8 (SAS Institute Inc, USA).

RESULTS

Demographics

There were 176 patients admitted to the Hospital for Sick Children with a diagnosis of acute KD over a three-year period who had the required three ECGs and echos available for analysis. The patient group studied included 116 boys (66%) with a median age of 3.1 years (range 0.2 to 15 years). The KD presentation was typical in 158 patients (90%), and the overall therapeutic measures included acetylsalicylic acid in 172 patients (98%), intravenous immunoglobulin in 169 patients (96%) and steroids in 11 patients (6%). The duration of illness before diagnosis was a mean $\pm$ SD of 6.7 $\pm$ 3.4 days. The initial echo was performed shortly after immunoglobulin administration (zero to three days). The subjectively defined maximal coronary artery involvement, as described in the comments of the echo report, showed no involvement in 81 patients (46%), ectasia alone in 88 patients (50%) and aneurysms in seven patients (4%). The initial mean ejection fraction was 69 $\pm$ 6% without evidence of regional wall motion abnormalities in any patient.

Coronary artery measurements

The initial (maximal) dimensions at the time of presentation showed that the mean left main coronary artery (LMAIN) diameter was 2.5 $\pm$ 0.5 mm, the left anterior descending coronary artery (LAD) diameter was 2.0 $\pm$ 0.5 mm and the right coronary artery (RCA) diameter was 2.1 $\pm$ 0.6 mm. Coronary artery involvement with measurements greater than 2 SD above the predicted normal value (Z-score greater than 2) was initially found in 11 patients (6%) for the LMAIN, in 26 patients (15%) for the LAD and in 19 patients (11%) for the RCA.

TABLE 1
Independent factors associated with serial echocardiographic and electrocardiographic measurements*

Factor	Estimate (SE)	P
Greater Z-score of LVED		
Intercept	0.485 (0.075)	
Increased initial Z-score of LVED	0.360 (0.045)	<0.001
Shorter interval from KD diagnosis†	0.055 (0.016)	<0.001
Interaction of initial Z-score of LVED and interval from KD diagnosis†	-0.100 (0.012)	<0.001
Younger age at KD diagnosis (per year)	-0.040 (0.011)	<0.001
Greater QT interval dispersion		
Intercept	0.725 (0.098)	
Greater initial Z-score of QT dispersion	0.401 (0.045)	<0.001
Greater depth of S wave in lead V1‡		
Intercept	139.5 (60.4)	
Shorter interval from KD diagnosis†	39.8 (9.3)	<0.001
Greater initial depth of S wave in lead V1	0.773 (0.035)	<0.001
Interaction of initial depth of S wave in lead V1 and interval from KD diagnosis†	-0.023 (0.009)	0.01
Greater initial height of R wave in lead V6	0.074 (0.026)	0.006
Greater depth of Q wave in lead V6‡		
Intercept	95.6 (13.6)	
Shorter interval from KD diagnosis†	11.3 (1.6)	<0.001
Greater initial depth of Q wave in lead V6	0.716 (0.035)	<0.001
Interaction of initial depth of Q wave in lead V6 and interval from KD diagnosis†	-0.079 (0.007)	<0.001
Greater initial height of R wave in lead V6	-0.043 (0.008)	<0.001
Greater initial Z-score of the LAD	5.66 (2.63)	0.04
Greater height of R wave in lead V6‡		
Intercept	1045.6 (82.4)	
Shorter interval from KD diagnosis†	161.5 (17.2)	<0.001
Greater initial height of R wave in lead V6	0.285 (0.044)	<0.001
Interaction of initial depth of S wave in lead V1 and interval from KD diagnosis†	-0.114 (0.011)	<0.001
Greater initial Z-score of the LAD	38.1 (14.1)	0.008

*From mixed linear regression analysis of repeated measures from serial electrocardiograms and echocardiograms; the term 'greater' is used to imply that the measurement is larger in the presence of the defined risk factors, and not specifically to imply the presence of an abnormality; †Entered after logarithmic transformation; ‡Model includes adjustment for sex and age. KD Kawasaki disease; LAD Left anterior descending coronary artery; LVED Left ventricular end-diastolic dimension

Left ventricular end-diastolic dimensions

Factors associated with greater Z-score of the left ventricular end-diastolic dimension (LVED) during the study interval were sought using mixed linear regression analysis for repeated measures (Table 1). The baseline measurement for the LVED in the acute phase was a mean of 3.4 $\pm$ 0.5 cm, with a mean Z-score of 0.97 $\pm$ 0.98 (P <0.001 compared with normal). There was a significant decrease over time, which was greater in the early interval after KD. There was a significant interaction with the initial Z-score of the LVED, with greater decreases in those with greater initial Z-score (Figure 1). A greater Z-score at any time was also significantly related to younger age at KD onset (Figure 2). After controlling for these factors, the LVED Z-score was not significantly related to the initial Z-score of any of the coronary artery branches (RCA P =0.11, LMAIN P =0.15, LAD P =0.20).

QT dispersion analysis

A similar analysis performed for ECG variables (Table 1) revealed the initial mean QT dispersion to be 54 $\pm$ 23 ms, with a mean initial Z-score of 1.34 $\pm$ 1.71 (P <0.001 compared with normal; 28% with an initial Z-score of 2 or higher). There was no significant trend demonstrated over time. The only factor associated with greater Z-score of QT dispersion over the study interval was a greater initial Z-score of QT dispersion.

Figure 1) The progression of the left ventricular end-diastolic dimensions Z-score (ZLVED) over time following a diagnosis of Kawasaki disease (KD), as predicted from a multivariable regression model for a four-year-old patient with initial Z-scores of 1 for the left main coronary artery, right coronary artery and left anterior descending coronary artery using three different values for the initial ZLVED. Patients with a higher initial ZLVED showed a more rapid decline in their ventricular dimensions as opposed to those with a smaller initial ZLVED

Figure 2) The inverse relationship between the age at onset of Kawasaki disease (KD) and the left ventricular end-diastolic dimension Z-score (ZLVED). Patients who developed KD at a younger age had greater ZLVED during follow-up than older subjects

The initial Z-score of LVED was not significantly related to the Z-score of QT dispersion ($P=0.62$). The Z-score of QT dispersion was not significantly related to the initial Z-score of any of the coronary artery branches (RCA $P=0.45$, LMAIN $P=0.86$, LAD $P=0.48$).

S wave depth in lead V1

The depth of the S wave in lead V1 (Table 1) at baseline was 9.8 ± 4.9 mm and showed a significant increase over the study interval, with a greater initial increase after adjustment for both age and sex. There was a significant interaction with the initial depth, with greater increases in those having lower initial depth. The S wave depth remained nearly constant over time in those with the greatest initial depth (Figure 3). Greater depth of the S wave in lead V1 over the study interval was also significantly related to a greater concomitant height of the R wave in lead V6. The initial Z-score of LVED was not significantly related to the S wave ($P=0.16$). The depth of the S wave in lead V1 was not significantly related to the initial Z-score of any of the coronary artery branches (RCA $P=0.86$, LMAIN $P=0.92$, LAD $P=0.67$).

Figure 3) The progression of the S wave depth in lead V1 is predicted from a multivariable regression model for a patient with an initial R wave depth in lead V6 of 15 mm using three different values for the initial S wave depth. The depth of the S wave increased over time in general, but in those with the largest initial depth, values remained nearly constant over time. KD Kawasaki disease

Figure 4) The progression of the Q wave depth in lead V6 is predicted from a multivariable regression model for a patient with an initial R wave depth in lead V6 of 15 mm using three different values for the initial Q wave depth. The depth of the Q wave decreased over time in general, but in those with the smallest initial depth, values increased slightly over time. KD Kawasaki disease

Q wave depth in lead V6

The depth of the Q wave in lead V6 (Table 1) was initially 2.0 ± 1.4 mm and showed a significant trend toward decrease over the study interval, with a greater initial decrease, as adjusted for both age and sex. There was a significant interaction with the initial depth, with greater decreases in those having greater initial depth (Figure 4). A greater depth of the Q wave in lead V6 over the study interval was also significantly related to greater initial height of the R wave in lead V6. The initial Z-score of LVED was not significantly related to the Q wave ($P=0.86$). The depth of the Q wave in lead V6 was not significantly related to the initial Z-score of the LMAIN ($P=0.57$), but was significantly related to greater initial Z-score of the LAD ($P=0.04$) and lower initial Z-score of the RCA ($P=0.08$).

R wave height in lead V6

The initial height of the R wave in lead V6 (Table 1) was 15.3 ± 5.2 mm and showed a significant increase over the study interval, with a greater

initial increase after adjustment for both age and sex (Figure 5). However, there was a significant interaction with the initial height, with greater increases in those with smaller initial height. Initial Z-score of LVED was not significantly related to the R wave ($P=0.38$). The height of the R wave in lead V6 was not significantly related to the initial Z-scores of the LMAIN ($P=0.29$) and RCA ($P=0.31$), but was significantly related to greater initial Z-score of the LAD ($P=0.002$).

DISCUSSION

Noncoronary cardiac outcomes

Our study showed that increased LVED is greatest in the acute setting and is independent of coronary artery involvement. Similarly, this is true for associated ECG indexes of left ventricular status. From a cardiovascular standpoint, the coronary arteries are the most prominently affected vessels by KD. Clinically, children can develop coronary artery aneurysms, endocardial inflammation and conduction system abnormalities. Within the spectrum of disease, children can present with hemodynamic abnormalities secondary to myocarditis or pericarditis (often with effusion). These children require careful monitoring, and many require inotropic support until the inflammatory cascade settles, allowing normal cardiac function to resume. As a pancarditis, cardiac involvement has been reported to include valvular regurgitation of the mitral, aortic and tricuspid valves due to valvulitis, which may persist beyond the acute phase (12). Ventricular enlargement or dilation, along with wall motion abnormalities, has been recognized in the acute setting of KD in 50% to 70% of patients (7,13). This is thought to be caused by myocarditis, independent of any coronary artery abnormalities (7,14). Not only does myocarditis impair ventricular function in the acute setting, but it has also been shown to persist for up to one to three years after the onset of symptoms in untreated cases (5,15,16). With widespread use of intravenous immunoglobulin, it is uncertain whether histological changes of inflammation will resolve sooner, although this has been believed to be true (17).

Conduction and repolarization anomalies

We have shown that QT dispersion is increased in patients with KD and does not completely resolve within the first year of recovery. An ECG is useful for evaluating heart block, or seeking evidence of myocarditis, QRS amplitude changes, T wave changes or QT interval changes in the acute setting (18-20). It has also been noted that signal-averaged ECG late potentials are present in the acute and chronic phases of KD; their presence may indicate evidence of myocardial ischemia or old myocardial infarctions, and may reflect the presence of microvascular disease, ongoing inflammatory myocarditis and later cardiomyopathy (19). Reports of ventricular arrhythmias have been reported in the acute phase of KD independent of coronary artery involvement (21). Increased QT dispersion has been found to be associated with increased risk for ventricular arrhythmia in patients diagnosed with myocarditis. The lack of normalization of QT dispersion may indicate that intravenous immunoglobulin does not increase the rate of histological resolution, or possibly that subclinical histological damage is permanent. As has been suggested, there may be a chronic phase of inflammatory myocarditis associated with KD, which accounts for the persistence of abnormal ventricular indexes in some children (3), and may also affect depolarization and repolarization in a similar manner. In the chronic setting, abnormal conduction has been demonstrated in Japanese children, such that the proportion of ECG findings (most commonly, incomplete right bundle branch block and right axis deviation) in adolescent KD patients was three times higher than that in normal controls (22). Inflammation has also been demonstrated pathologically within the conduction system in autopsy specimens of patients diagnosed with KD (23).

Myocardial consequences

The relationship between ventricular echo or ECG findings and coronary artery involvement has not been previously described, and there

Figure 5 R wave height in lead V6 progression over time stratified by initial R wave height. KD Kawasaki disease

is little reported literature focused on myocardial consequences associated with KD. Echo abnormalities of left ventricular contractility and myocardial function in the acute phase have been shown to have accelerated recovery after administration of intravenous immunoglobulin (15). A significant increase in the level of cardiac troponin I has been documented in the acute stage of KD and suggests that acute myocarditis or myocardial cell injury begins in the early phase of the disease, and that myocyte injury or inflammation is likely to occur before the onset of definitive clinical symptoms and signs of myocarditis (24). Early signs of myocarditis or subclinical myocarditis can be seen on the ECG, as indicated by ST-T wave changes, arrhythmia or abnormal voltages. We have shown that greater Q wave depth in lead V6, reflective of left ventricular dilation, correlates with the initial and subsequent trends for echo dimensions of the left ventricle (20).

Limitations

Our results do not include any assessments of diastolic function. In the presence of normal systolic function, patients with evidence for subclinical dysfunction may demonstrate diastolic functional abnormalities only. The diastolic functional indexes in KD in the acute and chronic settings need to be assessed further to better understand the subclinical effects of this pancarditis. In addition, the standard of care in our institution is to treat all cases of KD with intravenous immunoglobulin, but this is unlikely to be a confounding variable.

CONCLUSIONS

Although systolic ventricular dysfunction may not be evident, subclinical ventricular dilation may be present and is independent of coronary artery involvement. Ventricular dilation improves but may not normalize in the convalescent phase, with ongoing repolarization abnormalities indicated by increased QT dispersion. Further study over longer follow-up periods is necessary to define the clinical implications of these findings.

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