Coronary Artery Dimensions in Febrile Children Without Kawasaki Disease

Juan-Carlos G. Muniz, MD, MSc*; Kirsten Dummer, MD*; Kimberlee Gauvreau, ScD; Steven D. Colan, MD; David R. Fulton, MD; Jane W. Newburger, MD, MPH

Background—Coronary artery (CA) dilatation on echocardiography is a criterion for treatment with intravenous immunoglobulin for incomplete Kawasaki disease (KD). However, CA dimensions for febrile children are unknown. We compared CA dimensions in children with febrile illnesses other than KD to those of normal afebrile children and to KD patients.

Methods and Results—We performed echocardiograms in 43 patients who met the following inclusion criteria: (1) age 3 months to 18 years, (2) daily fever >38°C for ≥96 hours, and (3) a diagnosis other than KD. These subjects had mean CA z scores greater than normative values (left main CA=0.66±0.75, P<0.001; right CA=0.28±0.81, P=0.03; left anterior descending CA=0.35±1.0, P=0.03). Maximum CA z score >2 was found in 2 subjects (osteomyelitis, Mycoplasma pneumonia). Among demographic and laboratory measures, only higher platelet count was associated with greater left anterior descending CA z scores (P=0.004) and maximum CA z score (P=0.03). Non-KD febrile subjects, compared with 144 KD patients, had smaller CA z scores (P=0.04, P<0.001, and P<0.001 for left main CA, right CA, and left anterior descending CA, respectively), and lower white blood cell count, erythrocyte sedimentation rate, and platelet count (all P<0.001). A maximum CA z score cutoff of 2.0 had specificity of 95% (95% confidence interval, 84%–99%) and sensitivity of 32% (95% confidence interval, 25%–41%) in distinguishing non-KD febrile from KD patients; for maximum CA z score of 2.5, specificity was 98% and sensitivity was 20%.

Conclusions—This pilot study found that mean CA dimensions in children with non-KD febrile illnesses are larger than those in normative afebrile subjects but smaller than dimensions in patients with KD. Future studies should augment the available data on CA dimensions in children with more severe febrile illnesses. (Circ Cardiovasc Imaging, 2013;6:239-244.)

Key Words: coronary aneurysm ■ coronary arteries ■ Kawasaki disease ■ pediatrics

Kawasaki disease (KD) is a vasculitis of unknown cause that can result in coronary artery (CA) dilatation and aneurysm formation and is now the leading cause of acquired heart disease among children in the United States. Classic diagnostic criteria for KD include 4 days of fever and at least 4 of 5 principal clinical features, including nonexudative conjunctivitis, erythema of the oral mucosa, rash, cervical lymphadenopathy, and extremity findings (redness of the palms and soles, swelling of the digits, or later subungual peeling). However, it is well recognized that a subset of patients with KD has an incomplete presentation; these patients have a risk for CA aneurysms that is at least as high as that among patients with complete criteria.

Clinical Perspective on p 244

In recognition of the challenges posed in the diagnosis of incomplete KD, the American Heart Association published recommendations in 2004 that included an algorithm for intravenous immunoglobulin (IVIG) treatment of the child with suspected incomplete KD. In the algorithm, CA dilatation of >2.5 SD above the mean for body surface area in normative data (ie, CA z score>2.5) may be used to prompt IVIG treatment, and milder dilatation (CA z score, 2.0–2.5) is 1 of 6 suggestive echocardiographic findings for KD. However, normal ranges for CA dimensions were derived from healthy afebrile children. Moreover, CA dilatation has been known to occur in various other inflammatory and infectious diseases, including Epstein-Barr virus infection, Rickettsial infection, and systemic-onset juvenile idiopathic arthritis. The distribution of CA dimensions for children with febrile illnesses other than KD has not been established.

In this pilot study, we measured CA dimensions in children with non-KD febrile illnesses and compared these with normative data derived from healthy afebrile children, as well as with CA dimensions of patients with confirmed KD. Our goal was to explore whether current recommendations for treatment of incomplete KD could be refined by determining the

Received July 5, 2012; accepted January 8, 2013.
From the Department of Cardiology at Boston Children’s Hospital, Boston, MA; and the Department of Pediatrics, Harvard Medical School, Boston, MA.
Current address: Juan-Carlos G. Muniz, MD, MSc, Division of Cardiology, Miami Children’s Hospital, Miami, FL.
Current address: Kirsten Dummer, MD, The Children’s Heart Clinic, Minneapolis, MN.
*Drs Muniz and Dummer contributed equally to this work.
Correspondence to Jane W. Newburger, MD, MPH, Department of Cardiology; Boston Children’s Hospital, 300 Longwood Ave, Boston, MA 02115.
E-mail jane.newburger@cardio.chboston.org
© 2013 American Heart Association, Inc.
Circ Cardiovasc Imaging is available at http://circimaging.ahajournals.org
DOI: 10.1161/CIRCIMAGING.112.000159
range of coronary dilation seen in children who have febrile illness other than KD.

Methods

Subjects
Subjects were enrolled at a single institution (Boston Children’s Hospital) between 2005 and 2008. All of the following criteria were required for inclusion: (1) age 3 months to 18 years, (2) daily fever >38°F for at least 96 hours, and (3) diagnosis other than KD. The latter could include a diagnosis of proven cause, or viral syndrome believed by a KD expert to have features that were incompatible with KD. Exclusion criteria were (1) clinical conditions that made CA imaging impractical, such as inability to change position; (2) a preexisting systemic disorder; (3) systemic hypertension; (4) a family history of hypertrophic or dilated cardiomyopathy; (5) weight for height >95th percentile or <5th percentile; or (6) known structural or functional heart disease. This cross-sectional study was approved by the Boston Children’s Hospital, Institutional Review Board. Written informed consent was obtained from parents or legal guardians; consent from patients was also obtained when developmentally appropriate. Of the potential subjects who met inclusion criteria, none met the above listed exclusion criteria or refused consent or assent.

For comparison, we reviewed data on patients diagnosed with KD during the study period who had echocardiographic data collected between days 4 and 16 of illness.

Data Obtained
Echocardiograms were performed without sedation no later than within 24 hours of the last documented fever. Imaging was focused on coronary dimensions. Whenever possible, we also performed a complete anatomic and functional assessment. Echocardiograms were performed using the Sonos 7500 and iE33 (Philips, Andover, MA). All studies (ie, for non-KD febrile subjects and KD patients) were interpreted by 1 of 10 faculty members in the Division of Noninvasive Imaging at our institution in the course of their daily reading of clinical studies, according to a standard protocol for coronary imaging described by de Zorzi et al. The LMCA was measured in the midpoint, distal to the flaring often seen near the aortic orifice and before the first bifurcation. The left anterior descending coronary artery (LAD) was measured distal to the bifurcation and before the first marginal branch. The right coronary artery (RCA) was measured in the relatively straight section of artery just after the initial rightward turn from the anterior facing sinus of Valsalva. Inter- and intraobserver variability for CA measurements in our laboratory were previously described. Z scores adjusted for body surface area were calculated using normative data.

Clinical and demographic data obtained as part of routine hospital care during a patient’s admission were recorded. Variables included sex, age, race, days of fever, clinical symptoms, microbiological test results, alanine aminotransferase, aspartate aminotransferase, C-reactive protein, erythrocyte sedimentation rate, hematocrit; hemoglobin; platelet count, and white blood cell count.

Statistical Methods
Mean CA dimension z scores for children with febrile illnesses other than KD were compared with those of healthy afebrile children (mean z score=0) using the 1-sample t test; 95% confidence intervals (CIs) were calculated. The Shapiro-Wilk test was used to assess normality of the distributions. Relationships between patient demographic and clinical characteristics listed in Table 1 and CA dimension z scores were assessed using linear regression analysis. The coefficient of determination (R²) quantified the amount of variability in the outcomes (z scores) explained by their linear relationship with each patient characteristic. Demographic and clinical variables and CA dimensions in febrile study subjects and patients with confirmed KD were compared using Fisher exact test for categorical variables and either the Wilcoxon rank sum test or the 2-sample t test for continuous variables. Subjects with missing data were excluded from individual comparisons. We made no adjustments for multiple comparisons because of the exploratory nature of this pilot study. Sensitivity and specificity for predicting KD were estimated to maximum CA z score cut points of 2.0 and 2.5; 95% binomial CIs were generated.

Results
Forty-four subjects with febrile illnesses other than KD were enrolled. Echocardiography could not be performed in 1 patient because of agitation. Of the remaining 43 children in whom echocardiograms were performed within 24 hours of documented fever, 24 (56%) were female. Seventeen patients (40%) defined their race or ethnicity as white, 10 (23%) as Hispanic, 7 (16%) as black, 3 (7%) as Asian, 1 (2%) as Indian, 1 (2%) as other, and 4 (9%) were unknown. The median duration of fever at the time of the echocardiogram was 6 days (range, 4–14). Their diagnoses were pneumonia (n=9), osteomyelitis (n=8), urinary tract infection (n=5), viral syndrome (n=5), Epstein-Barr virus infection (n=3), cytomegalovirus infection (n=2), bronchiolitis (n=2), and 1 each with a diagnosis of fever of unknown origin, croup, stomatitis, gastroenteritis, influenza, toxin-mediated illness (deemed by a KD expert to be not consistent with KD), scarlet fever, purulent otitis media, and periorbital cellulitis. The causative organism was suspected or confirmed to be bacterial in 37%, viral in 47%, and unknown in 16% of patients. None of these patients received treatment with IVIG.

Left main coronary artery (LMCA) measurements were available in 41 patients, and LAD and RCA measurements were available in 43 patients. Mean z scores for all 3 CA segments were significantly increased compared with established normal data (Figure 1); by definition, the mean z score for each CA segment is 0, with an SD of 1. The LMCA was the most increased (mean z score=0.66±0.75, P<0.001), followed by the LAD (mean z score=0.35±1.0, P=0.03), and RCA (mean z score=0.28±0.81, P=0.03). The mean maximum z score (zMax), defined as the larger of the proximal LAD and the proximal RCA z scores, was 0.71±0.85, P<0.001.

Despite the shift to the right in CA dimensions of patients with febrile illnesses other than KD, only 2 patients (5%) had a CA z score >2. The first was an 11-year-old male with osteomyelitis (LAD z score=2.8). On follow-up echocardiogram 8 days later, the LAD dimension had normalized. The second was a 7-year-old female with Mycoplasma pneumonia (LAD z score=2.1). No follow-up imaging is available for this patient.

The relationships between CA z scores and clinical and demographic data are shown in Table 1. Higher platelet count was associated with both LAD z score (R²=0.212, P=0.003) and with zMax (R²=0.114, P=0.035; Figure 2). No other clinical or demographic variables were significantly associated with CA z scores, with limited power in this small dataset.

The KD control group consisted of all patients diagnosed with KD during the study period who had echocardiographic data collected between days 4 and 16 of illness (n=144). In 1 additional KD patient seen during the study period, coronary measurements were technically inadequate because of patient
agitation. Measurements were available in 140, 142, and 141 patients for the LMCA, LAD, and RCA, respectively. Fifty-four (37%) of these patients were female; 82 (57%) defined their race or ethnicity as white, 19 (13%) as Asian, 11 (8%) as black, 8 (6%) as Hispanic, 14 (10%) as other, and 10 (7%) were unknown.

Compared with the febrile study group, the KD control group had a lower median age (3.3 versus 6.1 years, \( P < 0.001 \)) and body surface area (0.69 versus 0.99 m\(^2\), \( P < 0.001 \)), and similar duration of fever at the time of the first echocardiogram (median, 6 days; \( P = 0.56 \)). Mean \( z \) score values, summarized in Table 2, were significantly higher in KD patients than in the febrile study group for each CA (RCA 1.16±1.79 versus 0.28±0.81, \( P < 0.001 \); LMCA 0.96±1.09 versus 0.66±0.75, \( P = 0.04 \); LAD 1.52±2.59 versus 0.35±1.02, \( P < 0.001 \); \( z \)Max 1.94±2.43 versus 0.71±0.85, \( P < 0.001 \)). Patients with KD also had significantly increased erythrocyte sedimentation rate, white blood cell count, platelet count, and decreased Hb compared with the febrile study patients (Table 2).

Finally, we explored the effect of using a threshold for \( z \)Max of 2.0 versus 2.5 on sensitivity and specificity to determine their utility for discrimination of KD from other febrile illnesses. The use of a \( z \)Max cutoff of 2.0 resulted in a specificity of 95% (95% CI, 84%–99%) and sensitivity of 32% (95% CI, 25%–41%) in distinguishing the febrile study (non-KD) group from the KD control group. Increasing this cutoff to \( z \)Max of 2.5 resulted in a specificity

| Table 1. Demographic, Clinical, and Laboratory Characteristics of Study Patients and Their Relationship to \( z \) Scores |
|---------------------------------|-----------------|-----------------|-----------------|
| Variable                        | \( z \)Max       | \( z \)Max       | \( z \)Max       |
|                                 | Regression      | Regression      | Regression      |
|                                 | Coefficient \( R^2 \) | Coefficient \( R^2 \) | Coefficient \( R^2 \) |
| Female                          | −0.42 0.061 0.11 | −0.20 0.010 0.54 | −0.32 0.039 0.21 |
| Race/ethnicity (vs white)       | 0.89            | 0.009           | 0.055           |
| Black                           | −0.35 0.37      | −0.06 0.91      | −0.42 0.26      |
| Hispanic                        | 0.24 0.49       | 0.24 0.57       | 0.11 0.73       |
| Other                           | 0.43 0.22       | 0.13 0.76       | 0.14 0.68       |
| Age, y                          | −0.027 0.028 0.28 | −0.0014 0.0001 0.96 | −0.022 0.022 0.35 |
| Age (category) (vs ≥10 y)       | 0.068           | 0.009           | 0.044           |
| <1 y                            | 0.17 0.79       | 0.27 0.74       | 0.33 0.61       |
| 1–<5 y                          | 0.28 0.38       | −0.08 0.85      | 0.25 0.42       |
| 5–<10 y                         | 0.57 0.10       | 0.12 0.78       | 0.43 0.20       |
| Days of fever                   | 0.039 0.018 0.39 | 0.048 0.019 0.38 | −0.0025 0.0001 0.95 |
| Infection type (vs viral)       | 0.002           | 0.025           | 0.033           |
| Bacterial                       | 0.10 0.77       | 0.36 0.37       | −0.26 0.4       |
| Unknown                         | 0.08 0.83       | 0.08 0.86       | −0.39 0.26      |
| ESR, mm/h                       | 0.067 0.047 0.39 | 0.011 0.104 0.19 | 0.0035 0.015 0.62 |
| CRP, mg/dL                      | 0.03 0.053 0.33 | 0.064 0.179 0.06 | 0.0075 0.003 0.81 |
| WBC count, \( 10^9/\)mm\(^3\)  | 0.021 0.026 0.32 | 0.041 0.072 0.1 | −0.009 0.006 0.64 |
| Hgb, g/dL                       | 0.39 0.003 0.76 | −0.029 0.0009 0.86 | −0.045 0.004 0.71 |
| Hct, g/dL                       | 0.036 0.044 0.43 | 0.024 0.006 0.66 | −0.014 0.010 0.75 |
| Platelets, \( 10^9/\)mm\(^3\)  | 0.0021 0.121 0.030 | 0.0032 0.205 0.004 | 0.00007 0.0001 0.99 |
| Albumin, g/dL                   | −0.46 0.158 0.26 | −0.61 0.227 0.19 | −0.31 0.098 0.38 |
| ALT, U/L                        | 0.0029 0.092 0.24 | 0.0033 0.108 0.21 | 0.0016 0.032 0.49 |
| AST, U/L                        | 0.0048 0.070 0.30 | 0.0035 0.033 0.50 | 0.0031 0.031 0.50 |

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hct, hematocrit; Hgb, hemoglobin; and WBC, white blood cell.

Figure 1. Coronary artery \( z \) scores for 43 patients with febrile illnesses other than Kawasaki disease. Circles represent individual patient \( z \) scores. Triangles represent mean \( z \) score for each vessel, and the bars represent the 95% confidence intervals. LAD indicates left anterior descending coronary artery; LMCA, left main coronary artery; and RCA, right coronary artery.
Discussion

In this pilot study, we found that mean CA dimensions in children with febrile illnesses other than KD were significantly larger than those in normative afebrile subjects. We also found that mean CA dimensions for children with non-KD febrile illnesses were significantly smaller than those of controls with KD. Thresholds of 2.0 and 2.5 for the maximum proximal CA dimension (ie, $z_{\text{Max}}$) resulted in high specificities (95% and 98%, respectively), but poor sensitivities (32% and 20%, respectively) and hence high false-negative rates. Thus, despite the observed coronary dilation in patients with febrile illnesses other than KD, these data would argue against upward adjustment of the $z_{\text{Max}}$ threshold in KD because the risk of IVIG treatment is low and benefit of preventing coronary aneurysms is so high. Nonetheless, population-based studies with larger sample sizes of febrile patients would provide more precise estimates of specificity and allow calculation of positive and negative predictive values. Such information may be of particular diagnostic utility in patients with incomplete presentation.

We identified dilated LAD in 2 patients with bacterial infections, specifically osteomyelitis and pneumonia; the dilatation had resolved on follow-up echocardiography in 1 patient who underwent reevaluation. CA dilatation has not been previously reported in these conditions, but has been shown to occur in other infectious diseases, such as Epstein-Barr virus and Rickettsial infections.\textsuperscript{11,12} It has also been shown in other autoimmune disorders.\textsuperscript{8,10} Binstadt et al\textsuperscript{8} have documented CA dilatation in patients with systemic-onset juvenile idiopathic arthritis. Several of their patients were initially suspected of having KD, and some received treatment with IVIG. None of their patients developed CA aneurysms, and all of the CA dimensions normalized. The pathogenesis of CA dilatation remains unknown in these disease states, but may be related to higher myocardial oxygen demand caused by fever and tachycardia. The resultant increase in coronary blood flow occurs by compensatory dilation of the CAs.\textsuperscript{13} Another potential mechanism of coronary dilatation may involve pathogenic proteins that bind to the endothelial cells, activating common immune response pathways that produce cytokines and further cell damage.\textsuperscript{14–16}

Higher platelet count was associated with greater LAD dimensions in our non-KD febrile patients. Thrombocytosis is uncommon in the first week of KD; indeed, in early KD, thrombocytopenia rather than thrombocytosis is a risk factor for aneurysm formation.\textsuperscript{2}

In patients with KD, increased CA dimensions have been associated with younger age, lower albumin level, and longer duration of fever.\textsuperscript{17} Although these associations were not significant in our group of febrile children without KD, we had low statistical power to detect such relationships.

This study should be interpreted in light of additional limitations. The study was designed as a pilot study, and thus inferences are limited by its small sample size. We did not adjust for multiple comparisons because of the exploratory nature of this pilot study. The statistically significant relationship of higher platelet count to larger coronary dimension could have occurred by chance. We were unable to compare the effects of different types of infections on CA size. In addition, multiple sonographers and cardiologists were involved in performing and interpreting the echocardiograms. We did not perform tests of reproducibility in our study sample. However, the study took place at a single center with a high degree of concordance in imaging methods of the echocardiography technicians and faculty; normative data in febrile children used in the AHA guideline and Pediatric Heart Network were generated at this same center.\textsuperscript{2,17,18} Our article could not distinguish whether coronary dilation in children with febrile illnesses other than KD was related to a fever-induced increase in cardiac output, to circulating inflammatory factors, or to both. In our study, patients with febrile illnesses other than KD were older and had milder laboratory indices of systemic inflammation than those with KD. It is possible that a series of children with more serious infections and comparable severity of the systemic inflammatory response with those of KD patients would have yielded larger CA dimensions. Finally, our study did not include systematic follow-up of CA dimensions.

In summary, we found that body surface area–adjusted CA dimensions in patients with febrile illnesses other than

Figure 2. Linear regression of left anterior descending (LAD) $z$ score (A) and maximum $z$ score, defined as the larger of the proximal LAD and the proximal right coronary artery $z$ scores (B) versus platelet count.

of 98% (95% CI, 88%–100%) and sensitivity of 20% (95% CI, 14%–28%).
KD were larger than those in normal afebrile children, but smaller than dimensions in patients with KD. The CA z scores that have been incorporated into the recommendations for the evaluation and treatment of KD derive from afebrile children. Our study provides reassurance that CA dimensions in children with more severe febrile illnesses define the false-positive rate of the CA z score threshold of 2.0. Nonetheless, future studies should augment the available data on CA dimensions in children with severe febrile illnesses to define the false-positive rate of the CA z score threshold of 2.0 used in the American Heart Association treatment algorithm for suspected incomplete KD.

Sources of Funding
This work was supported in part by the Farb Family Fund.

Disclosures
None.

References
15. Printz BF, Sleeper LA, Newburger JW, Minich LL, Bradley T, Cohen MS, Frank D, Li JS, Margossian R, Shirali G, Takahashi M, Colan SD; Pediatric Heart Network Investigators. Noncoronary cardiac abnormalities are associated with coronary artery dilatation and with laboratory


### CLINICAL PERSPECTIVE

The 2004 American Heart Association statement on Kawasaki disease (KD) uses coronary dilatation as a criterion for intravenous immunoglobulin treatment in incomplete cases. However, normal ranges for coronary dimensions were derived from afebrile patients. It is not known whether fever caused by illnesses other than KD leads to coronary dilatation. We performed echocardiograms on patients with non-KD febrile illnesses and compared their coronary artery dimensions with those of both normal subjects and patients with KD. We found that coronary dimensions in non-KD febrile patients were larger than those in the normal population, but smaller than in patients with KD. Abnormally dilated coronaries were identified in 2 of the 43 non-KD febrile patients, one with Mycoplasma pneumonia, and the other with osteomyelitis. The algorithm for evaluation and management of atypical KD uses coronary artery z score cutoffs of 2 and 2.5 in its diagnostic criteria. In our study, these thresholds both had high specificity but low sensitivity for differentiating non-KD febrile patients from KD patients, producing high false-negative rates. Thus, our findings argue against upward adjustment of the coronary z score cutoffs recommended in the 2004 American Heart Association algorithm, because the risk of intravenous immunoglobulin treatment is low and benefit of preventing coronary aneurysms is high. In the future, population-based studies with larger sample sizes of febrile patients, especially those with severe systemic inflammation, should provide more precise estimates of specificity and allow calculation of positive and negative predictive values to aid in the management and treatment of patients with suspected incomplete KD.
Coronary Artery Dimensions in Febrile Children Without Kawasaki Disease
Juan-Carlos G. Muniz, Kirsten Dummer, Kimberlee Gauvreau, Steven D. Colan, David R. Fulton and Jane W. Newburger

Circ Cardiovasc Imaging. 2013;6:239-244; originally published online January 28, 2013;
doi: 10.1161/CIRCIMAGING.112.000159
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/6/2/239

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Imaging can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Imaging is online at:
http://circimaging.ahajournals.org//subscriptions/