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## **Coronary Artery Involvement in Children With Kawasaki Disease. Risk Factors From Analysis of Serial Normalized Measurements**

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# Coronary Artery Involvement in Children With Kawasaki Disease

## Risk Factors From Analysis of Serial Normalized Measurements

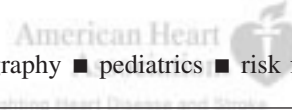
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**Background**—Most studies of coronary artery involvement and associated risk factors in Kawasaki disease have used the Japanese Ministry of Health dichotomous criteria. Analysis of serial normalized artery measurements may reveal a broader continuous spectrum of involvement and different risk factors.

**Methods and Results**—Clinical, laboratory, and echocardiographic measurements obtained at baseline and 1 week and 5 weeks after presentation were examined in 190 Kawasaki disease patients as part of a clinical trial of primary therapy with pulse steroids in addition to standard intravenous immunoglobulin. Maximum coronary artery  $z$  score normalized to body surface area was significantly greater than normal at all time points, decreasing significantly over time from baseline. A maximal  $z$  score  $\geq 2.5$  at any time was noted in 26% of patients. Japanese Ministry of Health dimensional criteria were met by 23% of patients. Significant independent factors associated with greater  $z$  score at any time included younger patient age, longer interval from disease onset to treatment with intravenous immunoglobulin, lower serum IgM level at baseline, and lower minimum serum albumin level.  $z$  Scores of the proximal right coronary artery were higher than those in the left anterior descending branch.

**Conclusions**—Analyses of serial normalized coronary artery measurements in optimally treated Kawasaki disease patients demonstrated that for most patients, measurements are greatest at baseline and subsequently diminish; baseline measurements appear to be good predictors of involvement during early follow-up. When a more precise assessment is used, risk factors for coronary artery involvement are similar to those defined with arbitrary dichotomous criteria. (*Circulation*. 2007;116:0000-0000.)

**Key Words:** Kawasaki disease ■ coronary disease ■ echocardiography ■ pediatrics ■ risk factors



Coronary artery involvement remains the most important complication after Kawasaki disease (KD) and involves a continuous spectrum ranging from no apparent involvement in the majority of patients to the presence of multiple giant aneurysms.<sup>1</sup> Involvement is assessed serially with echocardiography primarily by quantifying internal coronary artery diameters, although subtle qualitative features have been described.<sup>2,3</sup> Commonly used definitions of coronary artery involvement have relied on the Japanese Ministry of Health criteria, which dichotomously define abnormalities as a maximum absolute internal diameter  $>3$  mm in children  $<5$  years of age or  $>4$  mm in children 5 years and older, or a

segment 1.5 times greater than an adjacent segment, or the presence of luminal irregularity.<sup>4</sup> This definition contains subjective elements, incompletely accounts for patient size, and ignores any continuum or time course. More recently, regression equations based on measurements from nonfebrile normal children have been used to calculate  $z$  scores based on body surface area.<sup>5,6</sup> These allow a continuous measurement and assessment of the time course of involvement.

### Clinical Perspective p ■■■

Studies of risk factors associated with coronary artery involvement have also used a dichotomous definition usually

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consistent with the Japanese Ministry of Health criteria.<sup>7-19</sup> No study has used serial measurements of  $z$  scores to study the spectrum of involvement, time course of change, and associated risk factors. In addition, identified risk factors, such as younger patient age and male gender, laboratory abnormalities (such as higher white cell or neutrophil count, lower platelet count, higher C-reactive protein, higher erythrocyte sedimentation rate, lower serum albumin, and lower hemoglobin or hematocrit), treatment delay, and persistent or prolonged fever, have been inconsistent in their association with coronary artery abnormalities. Therefore, we sought to use serial assessments of normalized coronary artery dimensions to determine the spectrum and early time course of coronary artery involvement and, using these data, to define associated clinical and laboratory factors. This work represents a secondary analysis of data from the Pediatric Heart Network's Randomized Trial of Pulse Steroid Therapy in Kawasaki Disease.<sup>20</sup>

## Methods

The study design consisted of a randomized, double-blind, placebo-controlled multicenter trial, with randomization stratified by young age (<1 or  $\geq$ 1 year of age) and gender, balanced within center, with equal numbers assigned to each treatment arm.<sup>20</sup> Inclusion criteria for enrollment in the trial included diagnosis of typical KD by meeting modified criteria from recent American Heart Association guidelines,<sup>1</sup> presentation within 10 days of illness onset, and informed consent. Exclusion criteria for trial enrollment included prior treatment with intravenous immunoglobulin (IVIG) or systemic steroids, presence of another disease known to mimic KD, previous diagnosis of KD, and the presence of contraindications to steroid and aspirin use. Trial patients were randomized to receive either a single dose of intravenous methylprednisolone or an identical placebo before receiving conventional-dose IVIG and aspirin. For patients with persistent or recurrent fever, an additional dose of IVIG was given. Patients had standardized echocardiograms performed within 48 hours of enrollment (initial) and at 1 and 5 weeks after randomization. Echocardiograms were adjudicated in a core laboratory. To ensure a homogeneous study population, we excluded 9 of the 199 patients enrolled in the trial from the present analysis because they did not receive the assigned study drug ( $n=2$ ), were subsequently noted not to meet entry criteria ( $n=6$ ), or did not have any study echocardiograms ( $n=1$ ). Some patients were included in the analysis with initial echocardiograms performed after having received IVIG (34 at 1 day, 3 at 2 days, and 1 patient at 8 days after IVIG).

## Statistical Analysis

Coronary artery dimensions were normalized for body surface area as  $z$  scores (SDs from a predicted normal mean) based on nonlinear regression equations derived from a normal nonfebrile population.<sup>1</sup> The normal group comprised 221 healthy children aged 0 to 18 years seen in the noninvasive laboratory at Boston Children's Hospital for echocardiographic evaluation during the years 1987 to 2000 who had no evidence of structural or functional heart disease.<sup>21</sup> Acquired or congenital heart disease and other systemic disorders were excluded by review of the medical history, ECG, chest radiograph, and echocardiogram. Specific exclusion criteria included acute or chronic systemic disorder, hypertension, a family history of hypertrophic or dilated cardiomyopathy, and height, weight, or height for weight percentile outside the range of normal. The age distribution was 37% aged 0 to 1 year, 17% aged 1 to 5 years, 17% aged 5 to 10 years, 14% aged 10 to 15 years, and 6% aged 15 to 18 years. Nonlinear regression equations based on body surface area<sup>22</sup> were derived. The predicted value for a patient of a given body surface area can be obtained by solving the first exponential regression equation, and the associated SD of that predicted value can be

obtained by solving the second linear regression equation. The  $z$  score is obtained by dividing the difference between the actual measurement and the predicted measurement by the SD:

$$\text{LMCA} = 0.31747 \cdot (\text{BSA}^{0.36008}) - 0.02887, \text{SD} = 0.03040 + (0.01514 \cdot \text{BSA})$$

$$\text{pLAD} = 0.26108 \cdot (\text{BSA}^{0.37893}) - 0.02852, \text{SD} = 0.01465 + (0.01996 \cdot \text{BSA})$$

$$\text{pRCA} = 0.26117 \cdot (\text{BSA}^{0.39992}) - 0.02756, \text{SD} = 0.02407 + (0.01597 \cdot \text{BSA})$$

where LMCA indicates left main coronary artery, in centimeters; pLAD, proximal anterior descending coronary artery, in centimeters; pRCA, proximal right coronary artery, in centimeters; and BSA, body surface area, in meters squared.

For the purposes of analysis, only serial measures of the  $z$  scores of the pLAD and pRCA branches were used. Normal values do not currently exist for distal segments or the circumflex branch. Although normal values exist for the left main coronary artery, we chose to exclude this measurement from analysis because normal anatomic variations make its interpretation less reliable, and it is exceedingly rare to have enlargement of the left main coronary artery in KD without accompanying dilation of the pLAD. The same limitation relative to reliability applies to assessment of the circumflex branch and more distal segments, with regard to standardization of location of assessment and consistency of adequate visualization. Mixed linear regression analysis for repeated measures was used for the analysis. This technique is robust in that it makes use of both arterial branch measurements at all time points (rather than a maximal measurement from a single time point), uses the  $z$  score as a continuous rather than a dichotomous outcome measure, allows determination of trends over time from fever onset, and allows the identification of independent factors that are associated with higher  $z$  scores at any time or that may influence the time course of change. Variables that were tested are shown in the table in the online-only Data Supplement. Mean imputation was used to replace missing values for independent variables only. Of note, models created without imputation of missing values were very similar to those with imputation. Statistical analyses were performed with SAS statistical software version 9 (SAS Institute, Inc, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

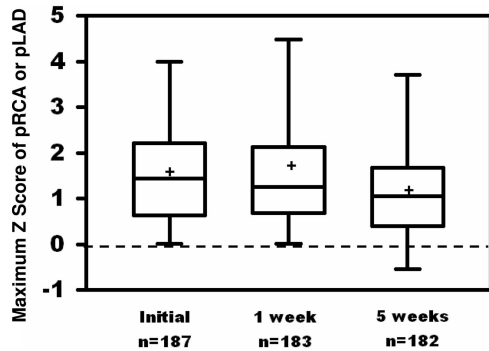
## Results

### Patient Characteristics

Of the 190 patients included in this analysis, 62% were males, with a mean age of 3.3 years (range 2 months to 12.3 years) and a mean duration of illness of  $6.6 \pm 1.4$  days at the time of enrollment. Race or ethnic group was white for 58%, black for 18%, Asian for 14%, American Indian or Alaskan Native for 2%, Native Hawaiian or other Pacific islander for <1%, more than 1 race or ethnic group for 7%, unknown for <1%, and Hispanic for 17% of subjects. Half (51%) were randomized to and received intravenous methylprednisolone.

Figure 1 shows the distributions of the maximum  $z$  score of the greater of the pRCA and pLAD over time. At initial assessment, the majority of patients had  $z$  scores well above a normal population predicted value of zero, with a median of 1.43 for the patients. Some decrease was noted at 1 and 5 weeks, although  $z$  scores remained elevated. At least 1 pRCA or pLAD  $z$  score  $\geq 2.5$  noted on at least 1 echocardiogram over the 5-week period was found for 26% of patients included in the analysis, and 5% had at least 1  $z$  score  $\geq 5$ .

By Japanese Ministry of Health criteria, 44 patients (23%) met dimensional criteria for involvement. This included 41 patients <5 years of age who had at least 1 dimension of a coronary artery segment >3 mm over the 5-week period



**Figure 1.** Maximum z score of either the pLAD or pRCA branch diameters according to time from randomization. Box encloses the 25th to 75th percentile, line represents the median, and tails represent the 5th and 95th percentiles. Cross represents the mean value. Outliers are not depicted, with minimum and maximum values as follows: initial assessment, -1.76, 9.73; 1 week, -1.07, 15.3; 5 weeks, -1.33, 15.3.

(including 3 patients with dimensions >4 mm), and 3 patients ≥5 years of age who had at least 1 dimension of a coronary artery segment >4 mm.

Of the 6 patients with any dimension >4 mm, 2 had dimensions >4 mm in either the pRCA or pLAD, 2 in the left main coronary artery only, and 1 in the distal left anterior descending coronary artery only. The remaining patient had dimensions >4 mm in nearly all branches, with increases in size noted from the initial to the 5-week assessment. One additional patient had an isolated aneurysm that measured 4 mm noted in the mid right coronary artery with no proximal aneurysm. No patient had a giant aneurysm, ie, with maximal internal lumen diameter ≥8 mm. Abnormal vessel tapering or luminal irregularities were not assessed.

**Time Trends From Initial Assessment**

Trends over time were explored. If the maximum z scores of the pRCA and pLAD were <2.5 at the initial echocardiogram, they did not increase above 2.5 for 94% of such patients at subsequent echocardiograms. If the maximum z score was ≥2.5 at the initial echocardiogram, the z score remained increased ≥2.5 over the 5 weeks of follow-up for 78% of subjects.

**Independent Factors**

Mixed linear regression analysis of repeated measures of z scores of the pRCA and pLAD demonstrated 6 independent risk factors associated with a greater magnitude of z score. A linear decrease in z score occurred from initial assessment over the 5 weeks of follow-up (Table). z Scores of the pRCA were significantly greater than those of the pLAD at all time points. Younger patient age at enrollment was independently associated with a greater z score at all time points. Figure 2A shows the independent relationship of age at enrollment with z scores. Least squares mean z scores decreased in a linear manner with increasing age category at enrollment. Additional factors independently associated with a greater z score at any time included greater number of days from disease onset to treatment with IVIG, a lower IgM level measured at initial assessment, and a lower minimum albumin level noted

**Independent Factors Associated With Higher z Score of the Diameter of the pLAD and pRCA Branches (n=190 Patients)**

Variable	Estimate (SE)*	P
Intercept	4.08 (0.69)	<0.001
pRCA (vs pLAD)	0.17 (0.06)	0.009
Shorter time from enrollment to echocardiogram (d)	0.010 (0.002)	<0.001
Younger age at enrollment (y)	0.14 (0.04)	0.001
Lower minimum albumin level (g/dL)	0.83 (0.17)	<0.001
Greater time from fever onset to treatment with IVIG (d)	-0.14 (0.06)	0.03
Lower serum IgM level at initial assessment (mg/dL)	0.005 (0.002)	0.007

\*From mixed linear regression analysis of repeated measures. No significant interactions existed between factors or between factors and time course. Mean imputation was used to replace missing values for independent variables. The intercept refers to the intercept of the multivariable regression equation with the y-axis and represents the modeled baseline value of z score, which is then influenced by the presence or absence of the value of the listed factors weighted by their respective parameter estimate.

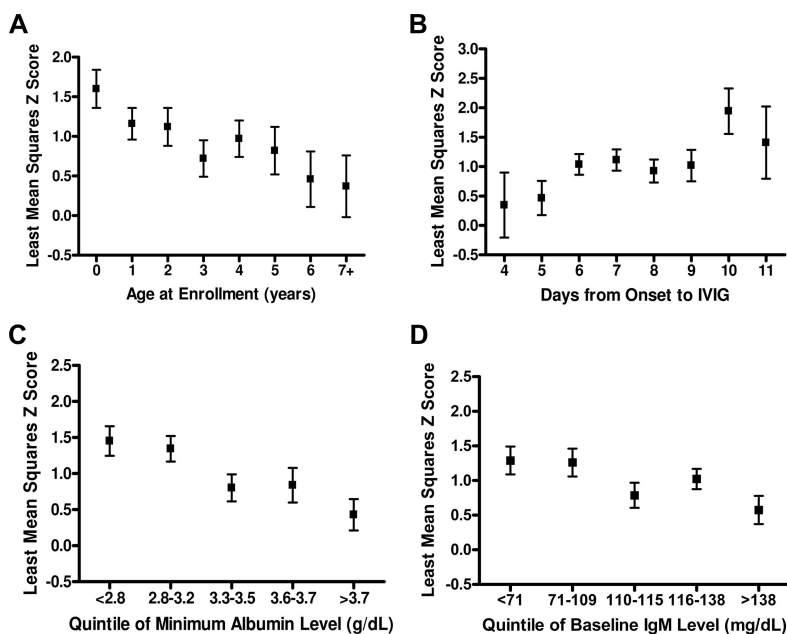
over the 5-week period. A similar analysis to that of age was performed with categories and quintiles and showed a linear relationship with no clear cut point that indicated increased risk for these variables (Figure 2B, 2C, and 2D). Likewise, various transformations of independent variables did not improve the fit of the model. No factor significantly influenced the noted time trend toward reduction in z score. Of note, the main clinical trial did not show a significant impact of the addition of pulse steroid therapy to IVIG on coronary artery outcomes, although a trend in favor of benefit was noted for those patients resistant to IVIG.<sup>20</sup>

**Discussion**

**Definitions of Coronary Artery Involvement**

We have defined a more precise spectrum of coronary artery involvement using serial normalized coronary artery dimensions and determined associated risk factors. In 1984, the Japanese Ministry of Health established the first definitions of coronary artery involvement in KD patients.<sup>4</sup> These criteria have been widely adopted in reporting the prevalence of coronary artery abnormalities, associated factors, and the effects of interventions. However, it is recognized that these definitions are arbitrary, fail to account for patient size, and reflect only the time point of maximal dimension. De Zorzi et al<sup>5</sup> explored the distribution of coronary artery dimensions, adjusted for body surface area as z scores using linear regression equations derived from a normal afebrile control population, in patients with KD whose arteries were classified as “normal” by Japanese Ministry of Health criteria. They noted that 27% of patients having no coronary artery involvement by Japanese Ministry of Health criteria had a least 1 coronary artery z score >2, or 2 SDs from normal based on body surface area. Involvement was maximal in the first 10 days of illness, similar to the present findings and other reports.<sup>6,23</sup>

As reported in the present study, attention to the continuous and varying nature of coronary artery dimensions may reveal



**Figure 2.** Independent influence of variables on serial measurements of z scores of the pLAD or pRCA branch diameters from any time after randomization early after acute KD. Values are least square means from mixed linear regression analysis adjusted for the factors shown in the Table. Error bars represent SE of the least squares mean from the regression models. A, Age at enrollment. B, Days from fever onset to IVIG treatment. C, Quintile of minimum albumin level. D, Quintile of initial IgM level.

a broader spectrum of involvement. Furthermore, long-term studies have suggested that coronary arteries that would be defined as having had no involvement based on Japanese Ministry of Health criteria may demonstrate functional abnormalities.<sup>24–26</sup> Thus, it is possible that these criteria are insensitive for identifying patients with more subtle involvement who may still be at increased risk for accelerated atherosclerosis and thus warrant ongoing assessment and counseling. In the future, more precise methods to detect mild degrees of coronary artery involvement may better define KD patients who should be monitored more closely for premature atherosclerotic cardiovascular disease.

### Risk Factors for Coronary Artery Involvement

Using serial assessments of dimensions, we defined 6 risk factors independently associated with a continuous normalized measure of coronary artery involvement. Although our assessment is more precise, the risk factors determined are similar to those previously reported with dichotomous definitions, particularly the Japanese Ministry of Health criteria applied at the time of maximal luminal dimension. Several studies have further focused on risk factors for aneurysms, particularly giant coronary artery aneurysms ( $\geq 8$  mm in diameter).<sup>11–13,15–18,27–29</sup> In examining serial z scores of coronary artery dimensions measured over the first 5 weeks after presentation, we defined the early time course of change and identified younger patient age, longer time to treatment, lower initial IgM level, and lower minimum albumin level to be significantly and independently associated with a higher z score at any time. These risk factors confirm the findings of previous studies that used Japanese Ministry of Health criteria.

Demographic, clinical, and management factors have been previously noted to be associated with coronary artery involvement. Demographic risk factors reported have included male gender,<sup>8,19,28,30</sup> race,<sup>8</sup> and younger patient age, particularly less than 1 year of age.<sup>8–10,15,16,19,30,31</sup> Older patient age

has been less consistently reported<sup>8,19,32</sup> and may be more related to delays in diagnosis and treatment. The absence or presence of particular clinical criteria has not been reported to be a risk factor, nor has the presence of concomitant infections<sup>33</sup> or arthritis.<sup>34</sup> Prolonged or persistent fever has been consistently reported as a risk factor,<sup>7,9–11,14,27</sup> as has recurrence of KD.<sup>19,35,36</sup> Management factors have been prominent, particularly delays in diagnosis and treatment.<sup>8,12,15,37,38</sup> Anderson et al<sup>37</sup> noted that delayed diagnosis was not significantly related to healthcare system factors but was related to dispersion over time in the development of clinical features. Early treatment has been debated as a risk factor,<sup>39,40</sup> although it may be a risk factor for unresponsiveness to IVIG.<sup>39</sup> Egami et al<sup>41</sup> studied risk factors for unresponsiveness to IVIG and noted many of the same risk factors as for coronary artery involvement.

There has been a great deal of focus on laboratory factors, and threshold values are suggested for clinical decision making in algorithms with regard to diagnosis and treatment.<sup>1</sup> Hematologic factors have included lower hemoglobin or hematocrit,<sup>7,10,14,16,27,30</sup> lower platelet count,<sup>7,30,42</sup> and higher white cell count, often with higher neutrophil or band components.<sup>7,10,13,15,16,30</sup> Burns et al<sup>43</sup> reported that higher  $\beta$ -thromboglobulin was significantly associated with aneurysm formation. Lower serum albumin has been a prominent risk factor,<sup>9,10,29,30</sup> and lower serum sodium and potassium<sup>12,16</sup> and higher alanine aminotransferase have been reported.<sup>12,16,17,39</sup> Inflammatory markers have been interesting, with higher C-reactive protein being an inconsistent risk factor.<sup>12,13,44</sup> There has been some interest in serum cytokines, with elevations in interleukin-6 and interleukin-8 reported as risk factors.<sup>45–47</sup> We noted that a lower IgM level at initial assessment was significantly associated with higher coronary artery z scores. Previous studies have reported that lower initial IgG level, adjusted for age, was a risk factor.<sup>48,49</sup> Later in the course of KD, higher IgG and lower IgA have been

reported to be significantly associated with coronary artery involvement.<sup>14,48</sup>

**Study Limitations**

The findings of the present study must be viewed in light of some potential limitations. The present study population did not include patients with incomplete presentations, those presenting beyond 10 days from fever onset, and those not treated with IVIG or other dosing regimens of IVIG. Thus, our study findings may not be completely generalizable to the total population of patients being identified with potential KD in clinical practice. Normalization as z scores was based on regression equations derived from observations in nonfebrile normal children. Normative data are not available for distal coronary artery segments. Thus, our analyses focused on normalized measurements of the pLAD and pRCA rather than the entire coronary artery tree. However, outliers were few and are reported from semiquantitative assessment, and distal arterial segments are rarely aneurysmal without at least some proximal dilation. Patients were not followed up beyond 5 weeks after presentation, and therefore, longer-term changes were not studied. The prevalence of severe coronary artery involvement was lower compared with other studies addressing associated factors, which either included more patients with aneurysms or focused on them specifically.

**Summary**

On the basis of the present results, we noted that for patients with typical KD treated in accordance with current guidelines within the first 10 days of illness, coronary artery dimensions are significantly increased in the first 5 weeks after presentation, although the prevalence of aneurysms is low. With serial normalized measurements, initial measurements appear to be good predictors of involvement during early follow-up, with patients whose initial z score is <2.5 maintaining that score during early follow-up. We defined 6 independent risk factors associated with our more precise analysis of a continuous spectrum of coronary artery involvement. The risk factors we noted are similar to those reported from studies using arbitrary dichotomous definitions of coronary artery involvement. Understanding the risk factors for coronary artery involvement in KD patients may facilitate the identification of low-risk children in whom extensive and frequent testing may be unnecessary, as well as high-risk children who may require closer monitoring and may be candidates for additional therapies.

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**Disclosures**

None.

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### CLINICAL PERSPECTIVE

Kawasaki disease is an acute, self-limited vasculitis of unknown cause associated with the development of coronary artery aneurysms in infants and children. Studies of risk factors for coronary artery involvement usually define involvement dichotomously as either present or absent based on measurement of maximal arterial diameters. The present study analyzed serial normalized measurements and noted that dimensions were maximal at baseline assessment at presentation and diminished thereafter but remained above normal in the majority over the 5-week period of observation. Associated risk factors were identified and were similar to those defined with arbitrary dichotomous criteria. The definition of coronary artery involvement has important implications for follow-up, and the identification of risk factors may distinguish those high-risk patients who might require increased surveillance or more aggressive treatment.