



# Progressive Coronary Dilatation Predicts Worse Outcome in Kawasaki Disease

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**Objective** To explore the implication of serial coronary changes on the late coronary outcomes in patients with Kawasaki disease (KD) with coronary aneurysms  $\geq 4$  mm.

**Study design** We performed a retrospective review of 78 patients with KD with large coronary aneurysms (1980-2013, male: 76.9%; 792 patient-years). Progressive coronary dilatation was defined for those with progressive enlargement of coronary arteries in 3 consecutive echocardiograms.

**Results** We studied 27 patients with KD with giant aneurysms ( $\geq 8$  mm) and 51 patients with KD with medium aneurysms (4-8 mm). All the giant and 43.1% of medium aneurysms persisted during the study period. For the patients with giant aneurysms, their 10-year freedom from acute myocardial infarction/cardiovascular death and all ischemia was 66% and 52%, respectively. The median intervals for the aneurysm diameters reaching their peak were 3.3 months (giant) and 0.25 months (medium), respectively. In patients with giant aneurysms, the 10-year freedom from ischemia was much lower in those with progressive coronary dilatation (28% vs 59%,  $P = .021$ ). In patients with medium aneurysms, the probability of 5-year persistence of aneurysm was much greater (67.2% vs 14.8%,  $P < 10^{-3}$ ) in those with progressive coronary dilatation. Male sex and intravenous immunoglobulin therapy were not associated with the late outcomes in the patients with KD who had aneurysms larger than 4 mm.

**Conclusions** In addition to coronary diameters 1 month after the onset of KD, progressive coronary dilatation at 2 or more months after diagnosis may be an indicator of duration, and the severity of vasculitis and adverse dilative remodeling were associated with worse late coronary outcomes. (*J Pediatr* 2016;171:78-82).

**K**awasaki disease (KD) has become the most common form of pediatric systemic vasculitis.<sup>1</sup> Despite intravenous immunoglobulin (IVIG) therapy, coronary arterial lesions occur in 5%-20% of patients with KD during the acute stage.<sup>2-6</sup> Coronary arterial lesions may persist and even progress to stenosis or obstruction. The coronary arterial lesions usually are classified into 3 subgroups (small [ $<4$  mm], medium [4-8 mm], and giant [ $\geq 8$  mm]) based on their diameters during the acute stage, or 1 month after the disease onset.<sup>2,3</sup> Such diameter-based severity is the most significant predictor for the late coronary outcome.<sup>4</sup> Giant coronary aneurysms usually don't regress and are likely to cause myocardial ischemia or even sudden death.<sup>4,7</sup> The 10-year survival rates of patients with giant aneurysms range from 92% to 96%.<sup>4,7,8</sup> One-half of the medium-sized coronary aneurysms may persist, and 14%-20% of them progress to stenosis.<sup>4</sup> Several studies,<sup>8-11</sup> however, demonstrated there were ongoing changes of coronary morphology (shape, diameters, composition, or wall thickness) in patients with KD with coronary arterial lesions after the acute stage. The changes in coronary arterial lesions toward maximal diameter beyond the acute stage may imply ongoing coronary vasculitis and dilative remodeling.<sup>8-10</sup> The clinical implications of these changes for late coronary outcome in patients with KD remains undefined. Therefore, we conducted a longitudinal study to delineate the clinical implications of coronary artery changes beyond the acute stage for the long-term outcome.

## Methods

The diagnosis of KD was made based on clinical criteria for KD.<sup>2,4</sup> All children received echocardiography during the febrile stage and the subacute phase (1 week, 3 weeks, and 2 months after fever onset, and the subsequent frequency varied depending on the severity of the coronary arterial lesions), except patients diagnosed before 1984. Coronary arterial lesions were defined as in previous studies<sup>3,4</sup>; however, only in cases in which coronary arterial lesions persisted for more than a month after onset of disease were considered coronary aneurysms.<sup>3</sup> The size of coronary aneurysms was classified as small ( $<4$  mm), medium (4-8 mm), and giant

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AMI	Acute myocardial infarction
CV	Cardiovascular
IVIG	Intravenous immunoglobulin
KD	Kawasaki disease

( $\geq 8$  mm).<sup>3,4</sup> Coronary arterial lesions and their regression were diagnosed on the basis of 2-dimensional echocardiography and confirmed with the use of computed tomography or angiography if indicated when the results of a 2-dimensional echocardiogram showed regression of medium-sized coronary aneurysms, or for the patients who exhibited symptoms of myocardial ischemia, or for regular follow-up of giant aneurysms every 3-5 years.<sup>4</sup> The study was approved by our Institutional Research Board.

We defined cardiovascular (CV) death as death attributable to myocardial infarction, heart failure, or sudden cardiac death. Acute myocardial infarction (AMI) was defined by a combination of typical chest discomfort, elevation of cardiac enzymes, and a typical electrocardiographic finding (ST segment-T wave changes, new left bundle branch block, or development of Q wave).<sup>12</sup> Low-dose aspirin was given for at least 6-8 weeks and until when echocardiography confirmed the regression of coronary lesions. Patients with KD with giant aneurysms received warfarin together with aspirin. Electrocardiogram was performed annually and whenever patients complained of chest tightness. Diagnosis of myocardial ischemia was made on the basis of ST-segment changes and/or stress radionuclear imaging results.

In this study, we reviewed 845 echocardiograms of the 78 enrolled patients with KD. Each measurement was performed by 1 cardiologist. For a randomly selected 10% of the echocardiograms, a second sonographer who was blinded to the first reading measured independently the coronary diameters in an off-line manner. The interobserver variability was tested by the use of intraclass correlation coefficient and by comparing the readings of the first and second sonographers. The interobserver reliability was 0.79, and the interobserver and intraobserver differences were 6.6%, and 6.1%, respectively.

Progressive coronary dilatation was defined as progressive dilatation seen in 3 consecutive echocardiograms. That is, the coronary diameter of the later study was larger than the previous one and the result of the third study should be 8% greater than the first one. We set an increase of "8%" for the definition of progressive coronary dilatation because: (1) A previous study<sup>13</sup> on the Taiwanese coronary Z score calculators showed interobserver difference was 7.1% for left main coronary artery, 5.8% for left anterior descending coronary artery, and 5.2% for right coronary artery; and (2) in the current study, the interobserver and intraobserver differences were 6.6%, and 6.1%, respectively.

### Statistical Analyses

We performed analyses using SPSS v11.5 (IBM, Armonk, New York). The data were expressed as mean  $\pm$  SD (medians with ranges), and we used the Mann-Whitney *U* test for 2-group comparisons. The  $\chi^2$  test was used to compare categorical data. For the time-related events and outcome variables, we used Kaplan-Meier estimates to draw event-free curves and tested their association with candidate

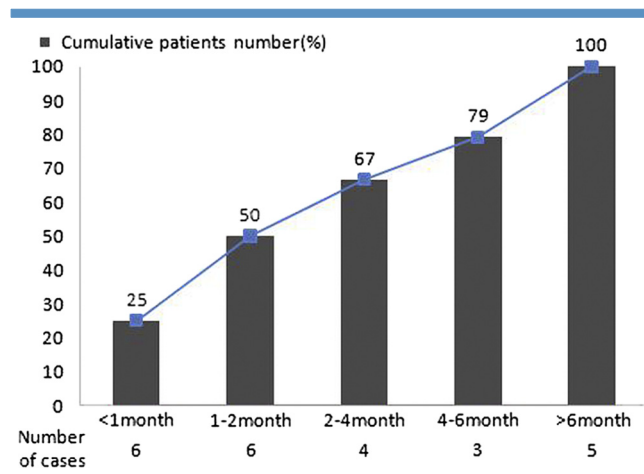
independent factors by using log-rank tests. To estimate regression probability, the follow-up period ended when the coronary arterial lesions regressed or patients did not attend scheduled follow-ups. Variables related to time-related events with  $P < .1$  in the univariate analysis were entered into the multivariate model. Statistical significance was set at  $P < .05$ .

## Results

Between 1980 and 2013, 1117 patients were diagnosed with KD (male/female = 687/430, 1.6), including 24 patients with atypical KD with coronary artery lesions. The age at diagnosis ranged from 1 month to 18 years (median 1.59 years). Coronary arterial lesions occurred in 38.6% of the patients during their acute febrile stages. Coronary aneurysms, defined as coronary arterial lesions that persisted beyond 1 month of the onset of KD, were noted in 201 patients (18.0%, male/female = 141/60). Of the 201 patients with KD with aneurysms, 27 (13.4%) patients had giant aneurysms ( $\geq 8$  mm), and 51 (25.4%) had medium-size aneurysms (4-8 mm). Male sex was significantly associated with coronary severity (small, medium, and giant) at onset of KD and 1 month later ( $P < .01$ ).

### Time to Reach the Peak of Coronary Aneurysm Diameters

The median intervals for the giant coronary aneurysms to reach their greatest size (8.0-14.1 mm) were 3.3 months, ranging from 0.33 to 8.53 months (Figure 1). The giant aneurysms stopped their progression within 1 month after the onset of KD in 6 patients and stopped progression within 2 months in 12 patients. For the patients with KD with medium-sized aneurysms, 33 did not have progression of their aneurysms 1 month after the onset of KD and 5 more didn't have further coronary



**Figure 1.** Distribution of time to reach the peak of aneurysm diameters in 27 patients with KD with giant coronary aneurysms.

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