Stenotic Lesions and the Maximum Diameter of Coronary Artery Aneurysms in Kawasaki Disease

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Objectives To determine the prevalence of subsequent stenotic lesions based on the maximum diameter of the largest coronary artery aneurysm in patients with Kawasaki disease and the threshold value of coronary artery diameter associated with risk of developing stenotic lesion.

Study design There were 214 patients (160 males) who had at least 1 aneurysm in a selective coronary angiogram (CAG) done <100 days after the onset of Kawasaki disease were studied. We measured the maximal coronary artery aneurysm diameter in 3 major branches in the initial CAGs. Branches were classified into 3 groups according to their maximal coronary artery aneurysm diameter: large, ≥8.0 mm; medium, ≥6.0 mm but <8.0 mm; and small, <6.0 mm. Subsequent CAGs were performed in the late follow-up period. We investigated the stenotic lesion in the follow-up CAGs, and evaluated the prevalence of stenotic lesion in each group based on body surface area (BSA) by the Kaplan-Meier method. Localized stenosis of ≥25% and complete occlusion were included as stenotic lesion in this study. We also determined the cutoff point for stenotic lesion.

Results The median interval from the initial CAGs to the latest CAG was 8 years, with a maximum of 32 years. For a BSA of <0.50 m^2, the 20-year prevalence of large and medium stenotic lesions was 78% (n = 62; 95% CI, 63-89) and 81% (n = 40; 95% CI, 63-89), respectively. For a BSA of ≥0.50 m^2, large and medium stenotic lesions were 82% (n = 75; 95% CI, 67-91) and 40% (n = 56; 95% CI, 20-64), respectively ($P < .0001$).

Conclusion The cutoff points of the coronary artery diameter within the first 100 days after the onset of Kawasaki disease leading to a stenotic lesion in the late period, were a diameter of ≥6.1 mm with a BSA of <0.50 m^2 and a diameter of ≥8.0 mm with a BSA of ≥0.50 m^2. Those cutoff points would have corresponded with a Z score of at least 10 on 2-dimensional echocardiography. Careful follow-up and antithrombotic therapy should be provided to patients who meet these criteria. *(J Pediatr 2017;■■:■■-■■).*

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Kawasaki disease (KD), first described in 1967, is an acute febrile disease that can lead to coronary artery aneurysm (CAA). The appearance of CAA affects the outcome in patients after KD. To prevent CAA, various treatments have been used over the last 50 years. Steroids were tried in 1970, and aspirin was used from the late 1970s to the early 1980s. Since the mid-1980s, intravenous immunoglobulin has remarkably decreased the prevalence of CAA. Unfortunately, there is no definitive treatment for intravenous immunoglobulin–resistant cases.

The prevalence of a large aneurysm (≥8.0 mm) has decreased to <0.5% in a recent national survey of Japan.[1] The CAA changes morphologically in the late period after acute KD. Most small CAA regress, whereas large CAA may persist, or evolve into stenotic lesion, which may cause a cardiac event. In 2005, we reported that dilatation of >6.0 mm produces a high probability of irreversible change in the coronary arterial wall, leading to subsequent stenotic lesions.[2] Because >10 years have passed since those studies, we investigated the prevalence of stenotic lesions based not only on the degree of maximal CAA diameter in the coronary angiograms (CAG) obtained immediately after KD, but also the impact of body surface area (BSA) at the initial CAG, to clarify the maximal CAA diameter leading to a stenotic lesion.

2DE	2-dimensional echocardiography
AUC	Area under the curve
BSA	Body surface area
CAA	Coronary artery aneurysm
CAG	Coronary angiogram
CAL	Coronary artery lesion
KD	Kawasaki disease
LAD	Left anterior descending artery
LCX	Left circumflex
RCA	Right coronary artery

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Methods

The diagnosis of CAA has recently been facilitated by the application of noninvasive methods such as 2-dimensional echocardiography (2DE), computed tomography angiography, and magnetic resonance angiography. However, until the 1990s, selective CAG by cardiac catheterization was the only method for the precise diagnosis of coronary artery lesion (CAL). There were 579 patients with CALs who had previously undergone CAG between 1978 and 2011 in our institution. We reviewed 214 patients (160 males and 54 females) (**Table I**; available at www.jpeds.com) who had had ≥1 CAA caused by KD in the initial CAG performed <100 days from the onset of KD and had undergone follow up CAGs ≥2 times. The number of patients per decade of the initial CAG was 16 patients in 1978-1979; 113 patients in 1980-1989; 55 patients in 1990-99; and 30 patients in 2000-2011 . For this study, the final diagnosis of KD and CAA was based on diagnostic guidelines prepared by the Japanese Circulation Society.[3,4] The age at acute KD episode ranged from 2 months to 13 years (median, 23 months). Initial CAG was performed from 20 to 99 days (median, 59), and BSA at the initial CAG was 0.31-1.63 m^2 (median, 0.52). The treatment of acute KD is shown in **Table I**. In our institution, aspirin, 1-2 mg/kg, as an antiplatelet agent was usually administered to patients with CAL. In addition, warfarin was added in patients with large aneurysms (≥8.0 mm). If the CAA had regressed in the follow-up CAG, medication was stopped. Treatment in the late period consisted of antiplatelet agents in 213 patients (99%) and warfarin in 47 patients (22%). The duration of medication ranged from 1 month to 38 years (median, 10 years).

We retrospectively investigated the prevalence of stenotic lesion in the follow-up CAG, based on the degree of the maximal CAA diameter at each branch and BSA in the initial CAG. The ethical committee of our institution approved this retrospective study.

Two hundred thirteen patients underwent a second CAG after an interval of 1 year. Only 1 patient without a second CAG had died, and his CAGs had been done immediately after his death. Subsequent follow-up CAGs were performed at 3- to 5-year intervals depending on the previous findings until the middle of the 2000s. If the coronary aneurysm regressed, subsequent CAGs were not performed. However, such patients were followed in the outpatient clinic by noninvasive imaging, including 2DE and computed tomography angiography. Further, treadmill testing and radioisotope myocardial perfusion scanning were performed depending on CALs. If progression of CAL was suspected on noninvasive imaging, CAG was considered at that time.

The maximum diameters of all aneurysms were measured in the initial CAGs, and their locations were noted. Right coronary artery (RCA) diameters were measured in the left anterior oblique 60° view, and the left anterior descending artery (LAD) and the left circumflex (LCX) diameters were measured in the right anterior oblique 30° or right anterior oblique 30° with caudal angulation of 30°. The diameters of the LCX were also measured in the left anterior oblique 60° view with 30° cranial angulation. We described the measurement of coronary arteries and the intraobserver and interobserver accuracy in a previous publication.[4,5] The diagnosis of CAA was determined by 2 pediatric cardiologists. Two different pediatric cardiologists had measured the maximal CAA diameter at each branch in the initial CAG. We divided the major branches into 3 groups determined by the maximal CAA diameter in each branch (large, ≥8.0 mm; medium, ≥6.0 mm but <8.0 mm; and small, <6.0 mm).

Stenotic lesions included localized stenosis of ≥25% and complete occlusion. The percentage of localized stenosis is defined as the degree of stenosis for near normal coronary arteries. Segmental stenosis implies the development of multiple new small vessels, which are speculated to occur after thrombotic occlusion of an aneurysm.[6] In this study, segmental stenosis was included in complete occlusion. If acute myocardial infarction occurred and the occluded branch was diagnosed on electrocardiogram or on CAG after the episode, it was considered a symptomatic complete occlusion. In contrast, complete occlusion first found in the follow-up CAGs are considered asymptomatic complete occlusion. We investigated the prevalence of stenotic lesion (localized stenosis of ≥25%, asymptomatic complete occlusion, symptomatic complete occlusion, the branch that had undergone coronary artery revascularization for stenotic lesion) in respective groups from the medical records and the follow-up CAGs. Coronary artery revascularization entailed coronary artery bypass grafting or percutaneous coronary intervention.

We considered the first appearance of stenotic lesion an event, and evaluated its prevalence overall and in the 3 major branches by the Kaplan-Meier method. Second, we analyzed the prevalence of stenotic lesions in the 3 groups based on the maximal CAA diameter. Further, normal coronary arteries diameter in children differed by body size. However, there was no normal value for children in CAGs. Because we could not base our analysis on the *Z* CAGs score, we divided them into 2 groups based on BSA. BSA was calculated using the Haycock formula. One group had a BSA of <0.50 m^2, and the other group had a BSA of ≥0.50 m^2. Third, we determined the prevalence of stenotic lesions in the groups based on the maximal CAA diameter in each branch and BSA in the initial CAGs. Fourth, we determined the cutoff points, which were the threshold value of coronary artery diameter in the initial CAG at risk of developing stenotic lesion in the late period.

Japanese normal values of coronary artery diameters by 2DE were reported, including *Z* score corrected by BSA.[7] Finally, we speculated about the prevalence of stenotic lesion in the values corresponding with the *Z* score measured by 2DE. Furthermore, the cutoff points corresponding with the *Z* score measured by 2DE leading to a stenotic lesion in the late period were calculated.

Statistical Analyses

Statistical analysis was performed using JMP 10 (SAS Institute Inc, Cary, North Carolina). Measurements are

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