

Incidence of Stenotic Lesions Predicted by Acute Phase Changes in Coronary Arterial Diameter During Kawasaki Disease

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Abstract. To clarify the incidence of stenotic lesions according to the coronary arterial diameter in the acute phase, we investigated 190 patients with coronary arterial lesions who underwent an initial coronary angiogram (CAG) less than 100 days after the onset of Kawasaki disease. The largest diameters of the major branches were measured in the initial CAGs. The diameter of the large group was ≥ 8.0 mm, that of the medium group was ≥ 6.0 mm but < 8.0 mm, and that of the small group was ≥ 4.0 mm but < 6.0 mm. There were 121 patients in the large group, 85 in the medium group, 77 in the small group. We investigated the stenotic lesions in the follow-up CAGs and evaluated the incidence of stenotic lesions in each group by the Kaplan–Meier method. The mean interval from the initial CAGs to the latest CAG was 97 months. The incidence of stenosis at 5, 10, and 15 years in the large group was 44, 62, and 74%, respectively. In the medium group the corresponding values were 6, 20, 58%, respectively. None of the patients in the small group developed stenotic lesions. Dilatation of more than 6.0 mm produces a high probability of irreversible change in the coronary arterial wall, leading to subsequent stenotic lesions.

Key words: Kawasaki disease — Coronary artery disease — Stenotic lesions

Although 35 years have passed since the first description of Kawasaki disease (KD), its long-term prognosis remains unclear [8, 9]. Although some reports of the midterm fate of coronary arterial lesions after KD exist, the incidence of stenotic lesions previously reported is that of the whole coronary arterial distribution [1, 5–7, 13, 16, 18], and it is generally accepted that aneurysms exceeding 8.0 mm evolve

into stenotic lesions [11, 21]. However, it is questionable how large an aneurysm results in a stenotic lesion. Stenotic lesions are the most important coronary arterial lesions due to KD because they induce myocardial ischemia and myocardial infarction, and myocardial infarction highly influences the prognosis [17]. We speculated that the fate of coronary arterial lesions, including the development of coronary stenosis after KD, relates to the degree of coronary arterial dilatation during the acute phase. Therefore, we tried to clarify the incidence of subsequent stenosis and the incidence of regression of coronary dilatation according to the coronary arterial diameter during the acute phase in both branch lesions and bifurcation lesions. Such data should clearly indicate the stratification of coronary arterial lesions and help the long-term management of patients with coronary arterial lesions due to KD.

Patients and Methods

Patient Population

We investigated 190 patients with coronary arterial lesions who underwent an initial selective coronary angiogram less than 100 days after the acute onset of KD. All were seen since 1978. All patients gave informed consent for selective coronary angiography, and all patients had coronary artery dilatation ≥ 3.0 mm in one or more branches and had undergone coronary angiography at least twice. There were 142 males and 48 females. The age at the onset ranged from 3 months to 13 years. The mean age at the onset of KD was 33 ± 30 months. The distribution of patients by age of onset was as follows: 0 year, 59; 1 year, 37; 2 years, 32; 3 years, 15; 4 years, 17; 5 years, 11; 6 years, ≤ 19 . A total of 160 patients (84%) were younger than 5 years old at the age of onset.

With regard to treatment during the acute phase of KD, 86% of patients received aspirin, and intravenous immunoglobulin was administered in 40% at a dose of 1–2 g/kg.

During the follow-up period, 90% of patients received antiplatelet agents, and 26% received warfarin. Aspirin dosage used was 1.5–3.0 mg/kg. When aneurysms of both coronary arteries regressed, the drugs were discontinued (46% of patients).

Methods

The mean interval from the onset of KD to the initial coronary angiogram was 58 ± 20 days. All patients underwent a second coronary angiogram after an interval of 1 year. Subsequent follow-up coronary angiograms were performed at 3- to 5-year intervals depending on the previous findings. If the coronary aneurysm regressed, subsequent coronary angiograms were not performed. Such patients were followed in the outpatient clinic by noninvasive imaging, including cardiac echocardiography and electron beam computed tomography. If coronary arterial lesions were suspected on noninvasive imaging, coronary angiography was considered at that time. However, for acute phase giant coronary aneurysms with apparent regression, coronary angiograms were still performed in the late period up to more than 10 years later. The mean number of coronary angiogram studies was 4 ± 2 , with a mean interval from the onset of KD to the latest coronary angiogram of 96.9 ± 72.3 months. The maximum interval was 250 months.

We categorized branch stenotic lesions and their regression in the follow-up coronary angiograms in groups based on the coronary arterial diameter in the initial coronary angiogram. We assessed localized aneurysms at the bifurcation of the left coronary artery separately from the major branches because of their characteristics. In this study, a bifurcation lesion indicates an aneurysm at the bifurcation of the left coronary artery that does not extend into the left anterior descending artery or the left circumflex.

We considered the first appearance of stenosis an event and evaluated its incidence in each group by the Kaplan–Meier method, which we also used to evaluate the incidence of regression of coronary dilatation in each group. The data were compared by the Cox–Mantel examination, and a significant difference was accepted as being less than 5%.

For this study, a stenotic lesion was defined as localized stenosis $\geq 25\%$, segmental stenosis, or complete occlusion. If acute myocardial infarction occurred and the occluded branch was diagnosed on electrocardiogram or on angiogram after the episode, it was considered as the event. For bifurcation lesions, we considered the appearance of a stenotic lesion in the left anterior descending artery, the left circumflex, or the left main trunk as an event. Regression was defined as regression of all coronary aneurysms in the respective branches or at the bifurcation.

We measured the largest diameters of the right coronary artery and the left anterior descending and the left circumflex arteries in the initial coronary angiograms, as previously described [23]. These made up the branches groups. The diameters of the right coronary artery were measured in the left anterior oblique 60° view, whereas the diameters of the left anterior descending artery and the circumflex were measured in the right anterior oblique 30° or right anterior oblique 30° with caudal angulation of 30° . The diameters of the circumflex were measured in the left anterior oblique 60° view with 30° cranial regulation. Bifurcation lesions of the left coronary artery were measured in a right anterior oblique 30° view with caudal 30° angulation. The measured diameters are shown in Fig. 1. The measured optimal angiogram was selected by both observers. The maximum diameters were measured using a software program (Siemens Ancor Version 2.3.1). Measurements by each observer and between observers were reproducible with high correlation coefficients, as previously published [23].

Branch and bifurcation lesions were classified into three groups according to their largest diameter. The diameter of the large group (L) was ≥ 8.0 mm. That of the medium group (M) was ≥ 6.0 mm but < 8.0 mm, and that of the small group (S) was ≥ 4.0 mm but < 6.0 mm. For branch lesions, the numbers in the

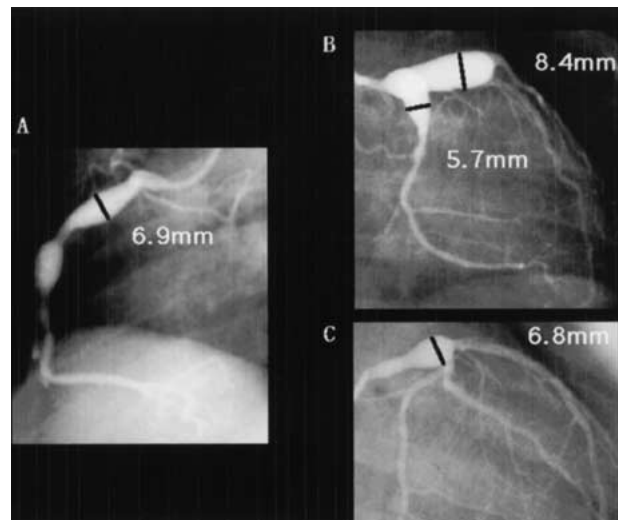


Fig. 1. Measurement of coronary arterial diameter in the initial angiogram. (A) Right coronary artery. (B) Left anterior descending artery and left circumflex artery. (C) Bifurcation lesion of the left coronary artery.

respective groups were as follows: L, 121; M, 85; and S, 77. For left bifurcation lesions, the numbers in the respective groups were as follows: L, 18; M, 25; and S, 34. The number of patients in the branch group in which the diameter was ≥ 3.0 mm but < 4.0 mm was 59, and for bifurcation lesions there were 9 patients. The mean intervals from the onset of KD to the latest coronary angiogram for the respective groups are shown in Table 1. The unpaired *t* test was used to compare the medium group with the large group for branch lesions. One-factor analysis of variance was used to compare groups for the bifurcation lesions. A significant difference was accepted as being less than 5%.

Results

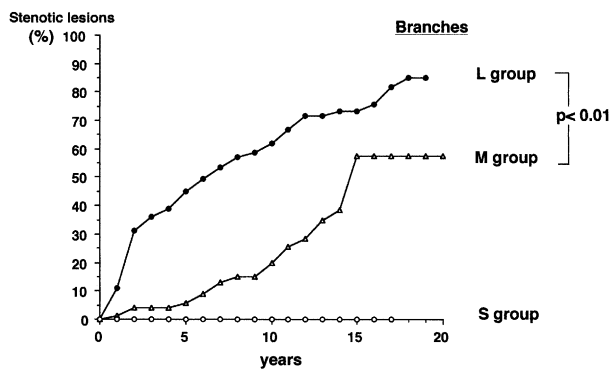
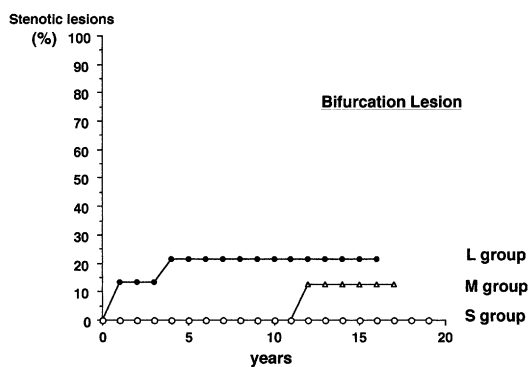
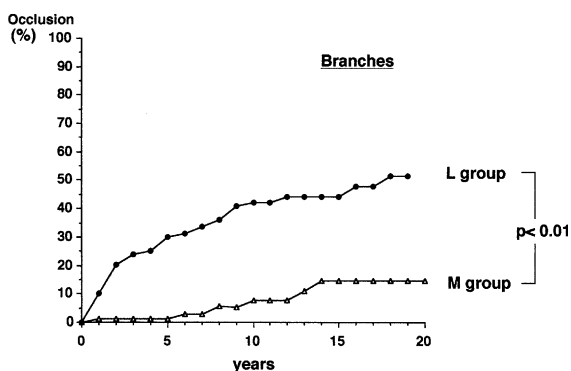
For the branches, the incidence of stenotic lesions in the respective groups is shown (Fig. 2). The incidence of stenotic lesions at 5, 10, and 15 years in the large group was 44, 62, and 74%, respectively. The incidence of stenotic lesions at 5, 10, and 15 years in the medium group was 6, 20, and 58%, respectively. The incidence of stenotic lesions in the large group is significantly greater than that in the medium group ($p < 0.01$). No aneurysms < 6.0 mm in diameter in both the branch group and the bifurcation group developed stenotic lesions. The threshold diameter for acute phase coronary aneurysms leading to subsequent stenosis was 6.0 mm.

The incidence of complete occlusion in the branches in the respective groups is shown Fig. 3, and at 5, 10, and 15 years in the large group it was 30, 43, and 45%, respectively. In the medium group; at 5, 10, and 15 years it was 1, 8, and 15%, respectively. The incidence of occlusion in the large group is significantly greater than that in the medium group ($p < 0.01$).

Table 1. Groups based on coronary artery diameter in the acute phase

Diameter (mm)	Group	n	RCA	LAD	LCX	Interval from the onset to the latest coronary angiogram (months)	
						Mean	SD
Branch group							
≤ 3.0 but < 4.0		59	18	19	22	72	65
≤ 4.0 but < 6.0	Small	77	31	29	17	83	68
≤ 6.0 but < 8.0	Medium	85	38	35	12	112	71
≤ 8.0	Large	121	65	45	11	117	73
Bifurcation lesion							
≤ 3.0 but < 4.0		9				120	88
≤ 4.0 but < 6.0	Small	34				91	74
≤ 6.0 but < 8.0	Medium	25				102	71
≤ 8.0	Large	15				110	74

RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery.

**Fig. 2.** Incidence of coronary stenotic lesions based on coronary diameter in the acute phase (branches).**Fig. 4.** Incidence of coronary stenotic lesions based on coronary diameter in the acute phase (bifurcation lesions).**Fig. 3.** Incidence of coronary arterial occlusion based on coronary diameter in the acute phase (branches).

For bifurcation lesions of the left coronary artery, the incidence of stenotic lesions in the respective groups is shown in Fig. 4. After 15 years, the inci-

dence of stenotic lesions in the medium and large groups was 13 and 23%, respectively. This was low compared with that of the branch groups.

The incidence of regression of coronary dilatation was also evaluated for both branch and bifurcation lesions. All aneurysms < 4.0 mm in diameter for both branch and bifurcation lesions regressed. Regression of coronary dilatation was evaluated in the branch group (Fig. 5). Its incidence at 5, 10, and 15 years in the small group was 74, 80, and 86%, respectively; in the medium group it was 26, 32, and 35%, respectively; and in the large group it was 6, 8, and 8%, respectively. The incidence of regression of coronary dilatation in the medium group was significantly greater than that in the large group ($p < 0.01$).

For bifurcation lesions (Fig. 6), after 15-year follow-up, the incidence of regression in the small, medium, and large groups was 80, 67, and 23%, respectively. The incidence of regression of coronary

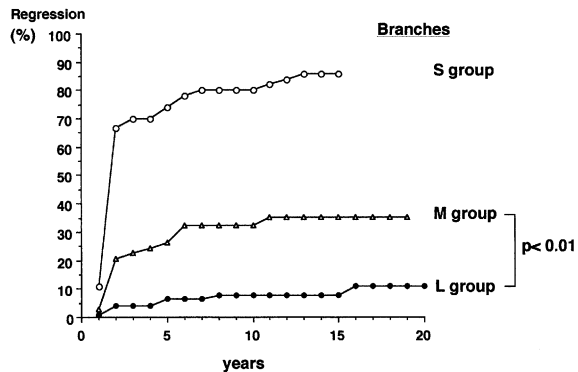


Fig. 5. Incidence of regression of coronary arterial dilatation based on coronary diameter in the acute phase (branches).

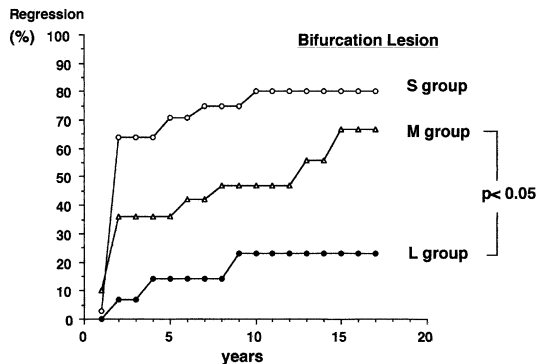


Fig. 6. Incidence of regression of coronary arterial dilatation based on coronary diameter in the acute phase (bifurcation lesions).

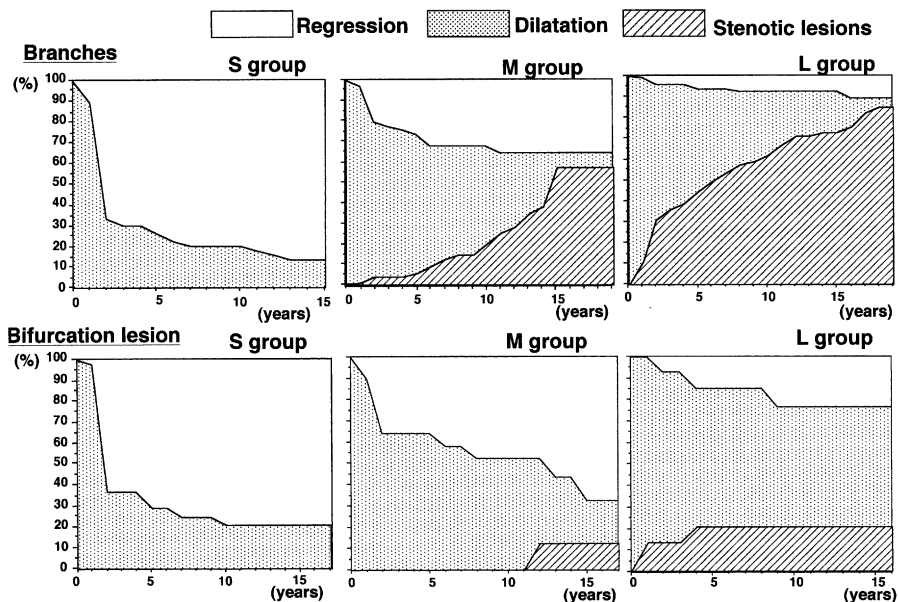


Fig. 7. Fate maps of coronary arteries based on coronary diameter in the acute phase.

dilatation in the medium group was significantly greater than that in the large group ($p < 0.05$).

We mapped the fate of coronary arterial dilatation based on the coronary arterial diameter in the acute phase from the previously mentioned data (Fig. 7). Of the patient population we studied, 186 patients are alive and 4 patients have died. Myocardial infarction occurred in 18 branches.

Discussion

In a national survey of KD in Japan in 1999 and 2000, 15,104 patients were reported. The survey revealed that coronary artery aneurysms developed in 17.16% of patients within 1 month of the onset of

KD. Giant aneurysms, aneurysms, and dilatations occurred in 0.46, 2.60, and 14.10% of patients, respectively. However, 1 month after the onset, aneurysms were present in only 5.67% (giant, 0.40%; aneurysms, 1.87%; and dilatations 3.40%) [24]. We estimate that late cardiac sequelae currently affect approximately 1% of KD patients.

The degree of coronary arterial dilatation most likely determines the subsequent fate of the vessel. Stenotic lesions include localized stenosis and complete occlusion. Localized stenosis is mainly caused by thickening of the vessel walls [3, 23], and we have shown a significant correlation between the diameters of coronary arteries in the acute phase of KD measured at coronary angiography and subsequent in-

tima-medial thickness observed more than 10 years later [13]. The degree of coronary arterial dilatation depends on the degree of destruction of the coronary arterial wall, and the extent of subsequent intimal thickening varies depending on the degree of injury during the acute phase, not only in a given patient but also in a given branch. Intimal thickening should be considered part of the reparative stage of the coronary arterial wall after the acute inflammation. The degree of destruction of the coronary arterial wall will determine the fate of the coronary arterial lesion. In a given patient, the coronary artery abnormalities change with time, and between patients the rate of change is variable.

The fate of coronary arterial dilatation can be divided into three major possibilities; persistent dilatation, regression, or progressive stenosis. The partition among the three major possibilities depends on the initial coronary artery diameter in the acute phase of KD. Acquired ischemic heart disease after KD is mainly caused by stenotic lesions [12]. However, persistent dilatation and regression of large coronary aneurysms can cause acute coronary infarction. We determined the fate of coronary arterial lesions, with our focus on the initial coronary artery diameter.

In the branch group, we found that dilatation of more than 6.0 mm results in a high probability of irreversible change in the coronary arterial wall, leading to subsequent stenosis or occlusion. In the large group, the incidence of stenosis was high at 5- and 15-year follow-up. In the medium group, although the incidence of stenosis was low at 5-year follow-up, it was much higher after 15 years. Although in most cases stenosis gradually develops through intimal thickening of the vascular wall over many years [3, 12, 15, 19, 22, 23], occlusion often occurred due to thrombotic events within approximately 2 years after the onset of KD. Impaired endothelial function that predisposes to thrombosis is possibly severe when coronary arterial dilatation exceeds 8.0 mm.

With respect to regression, after 15 years, its incidence in the small group, the medium group, and the large group was 86, 35, and 8%, respectively. The smaller the coronary artery diameter in the acute phase, the greater the probability of regression. As with stenotic lesions, the regression of coronary artery lesions depends on the original degree of coronary arterial dilatation.

In the large group, regression of the coronary aneurysm was uncommon. However, some large coronary aneurysms regressed. Whether large coronary aneurysms regress or not may be influenced by the affected segment or the length of the affected area.

Regression groups fall into two apparent subgroups. One is regression without intimal thickening,

which occurs in aneurysms < 4.0 mm and that regress within 1 year. All aneurysms < 4.0 mm in diameter in a coronary angiogram performed less than 100 days after the onset of KD regressed and did not develop cardiac sequelae. This observation supports the data of our previous intravascular ultrasound study that there is no late intimal thickening in aneurysms < 4.0 mm in diameter in the acute phase. Strictly speaking the term regression should be confined to this group.

The other subgroup is “apparent” regression with intimal thickening [19, 21, 23]. Apparent regression produces apparent normalization angiographically but with decreased coronary artery diameter due to intimal thickening. Recently, we observed acute myocardial infarction in patients with apparent regression. Although the cause of acute myocardial infarction is unknown, abnormalities of the coronary arterial wall probably predispose to the episode.

Acute stage aneurysms in KD usually involve the proximal segment of the coronary arteries. Bifurcation aneurysms of the left main coronary artery, which are often detected, are also characteristic of KD. In our study, thickening at the bifurcation of the left main coronary artery did not correlate strongly with the diameters of the coronary arteries in the first coronary angiograms [23].

For bifurcation lesions, the incidence of stenotic lesions was low compared with that of branch lesions. This may be explained by the difference in arterial types. Coronary arteries are muscular, whereas the ascending aorta is an elastic vessel. The most proximal portion of the left main artery is of a transitional structure. We speculate that the effect of acute vasculitis and its subsequent course of regression after the inflammation may differ in elastic vessels compared to muscular arteries. The characteristics of structure at the bifurcation may also explain the difference in behavior.

Usually, an aneurysm at the bifurcation > 10 mm in diameter is not localized to the bifurcation but extends into either the left anterior descending or the left circumflex arteries. We believe that the development of stenosis or occlusion in a bifurcation aneurysm is strongly dependent on the degree of involvement of the branches. In one patient with a long left main trunk, localized stenosis appeared in the left main trunk after a large aneurysm at the bifurcation.

We developed fate maps for coronary arterial dilatation based on a coronary arterial diameter ≥ 4.0 mm in the acute phase for branch and bifurcation lesions. These fate maps should facilitate the optimal follow-up and treatment of patients with coronary arterial lesions after KD. Currently, mea-

surement of the coronary arterial diameter in the acute phase by two-dimensional echocardiography is precise, and the value correlates highly with measurements by angiography. We believe that the results of this study will help in the prediction of the fate of coronary aneurysms by two-dimensional echocardiography without angiographic studies [2, 4].

When the diameters of the coronary aneurysms are the same in the medium group and the large group, the fate of the coronary aneurysms will not always be the same. The affected segment may determine the fate of the coronary artery due to additional factors. Furthermore, the factors that determine the fate of coronary aneurysms may derive from differences between patients. Clarification of such factors may be useful in the future in the treatment of sequelae due to KD.

Study Limitations

The study is limited by the fact that the treatment in the acute phase and in the late period varied in this patient population. However, the study entry point is the presence of coronary dilatation at the first angiogram. Although acute treatment may influence the incidence of aneurysms, it is unclear whether it influences their long-term fate. We think that our maps indicate the result of the treatment by antiplatelet agents. The treatment was similar to the usual treatment for patients with coronary arterial lesions due to KD. The influence of the antiplatelet agents on intimal thickening of coronary arterial wall in the long-term period is unclear. We stress that a primary goal of our study was to define the population of post-KD patients at greatest risk for late sequelae and we believe we have achieved this goal.

Although we used the absolute dimension in the initial coronary angiogram for the predictive value of stenotic lesions, correction of the dimension by body surface area might be better. Our study did not include patients who had coronary angiograms within 2 months of the onset of KD, and few patients had onset of KD at 3 months. The predictive value causing stenotic lesions in the aneurysms of the acute phase for these small infants must be investigated. Furthermore, we should consider a possible decrease in the diameter of the aneurysm within the first 100 days.

Conclusion

The threshold for coronary aneurysms causing stenosis is 6.0 mm in coronary angiograms performed less than 100 days after the onset of KD. We speculate that acute dilatation of more than 6.0 mm indi-

cates a high probability of irreversible change in the coronary arterial wall, leading to subsequent stenosis or occlusion.

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