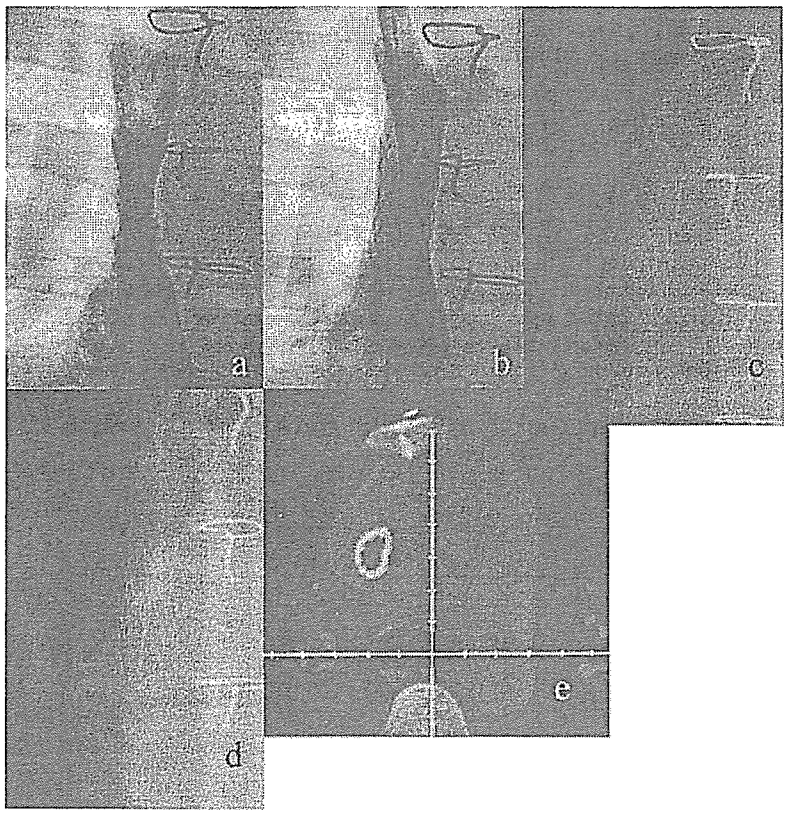

Fig. 5. Angiogram of superior vena cava before (a) and after (b) implantation of a P308 stent in case 2. Chest X-ray just (c) and 27 months (d) after stent implantation. Longitudinal compression was observed on chest X-ray at 27 months. e: CAT scan showed semicircular cross-section of the stent with flattening of the side adjacent to ascending aorta.

bifurcation are close to the ascending aorta, while in the setting of Williams procedure [8], when the transected superior vena cava is sutured to the right atrial appendage, the ascending aorta could be located close to the superior vena cava. As continuous pressure from the pulsation of the adjacent ascending aorta may cause late distortion of the stent, we should determine anatomical relationships between the lesion and the aorta before implanting a stent in such lesions. Careful follow-up is essential. As far as we could determine from the literature concerning long-term follow-up after stent implantation, including implantation for stenosis after the arterial switch operation, late stent distortion in such lesions is rare [12,13]. Consequently, other technical issues, such as manual crimping of the stent on the balloon and selection of the balloon diameter, may influence radial strength after implantation.

In conclusion, even the Palmaz stent, which is believed to have sufficient radial strength, may be distorted when implanted in a lesion adjacent to a pulsating aorta.

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CARDIOVASCULAR MEDICINE

Dilated coronary arterial lesions in the late period after Kawasaki disease

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See end of article for authors' affiliations

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Objectives: There are two types of late coronary dilated lesions after Kawasaki disease: new aneurysms and expanding aneurysms. The development of coronary dilated lesions late after Kawasaki disease was investigated.

Methods: Between 1978 and 2003, 562 patients with coronary arterial lesions underwent selective coronary angiography on at least two occasions.

Results: Of the 562 patients studied, 17 new dilated or expanding lesions were found in 15 patients (3%, 11 boys, four girls). The time of detection of new aneurysms after Kawasaki disease ranged from 1.9–19.2 years (median 11.4 years) and their diameters ranged from 2.0–6.5 mm (median 4.4 mm). Thirteen new aneurysms occurred in vessels in which previous aneurysms had regressed and all new aneurysms were associated with localised stenosis. A new aneurysm at the bifurcation or in the branches was seen in 14 (93%) and 13 were eccentric (87%). Of two expanding aneurysms, one involved the right coronary artery in one patient and the other the left anterior descending coronary artery. One expanding aneurysm increased from 4.4 mm to 19.5 mm over 17 years, and the other expanding aneurysm increased from 10 mm to 15 mm in one year.

Conclusions: Neither new nor expanding aneurysms have caused cardiac events. New aneurysms often develop as a pre-stenotic or post-stenotic dilatation secondary to localised stenosis. New and expanding aneurysms may be caused by haemodynamic factors in addition to the abnormality of the coronary arterial wall after severe acute vasculitis. Coronary arterial wall abnormalities were stenosis as well as, rarely, dilatation of the vessels in the late period. It is important to recognise that the changes of the coronary arterial wall persist late after regression of a large aneurysm.

The vasculitis of Kawasaki disease (KD) causes coronary aneurysms in about 10% of patients early after the onset.[1] Aneurysms usually change their shape after the acute phase, but some may persist for years whereas others either regress or evolve into stenotic lesions.[2–4] Usually, the diameters of persistent aneurysms may increase slightly because of somatic growth or they may decrease because of intimal thickening of the vascular wall.[5–8] In the late period of KD either new aneurysms or expanding aneurysms are unusual but have been reported.[9–12] We investigated the characteristics of the dilated lesions and their time of appearance and speculate about their cause.

PATIENTS AND METHODS

Between 1978 and 2003, after giving informed consent, 562 patients with coronary arterial lesions underwent selective coronary angiography on at least two occasions. The protocol was as follows. Coronary angiography for patients with coronary arterial lesions was performed immediately after the acute phase of KD. All patients underwent a second coronary angiography after one year and subsequent follow up coronary angiography was done at 3–5 year intervals depending on the findings. If the aneurysms regressed, subsequent coronary angiography was not done but the patients were followed up in the outpatient clinic by non-invasive imaging including echocardiography and electron beam computed tomography. If coronary arterial lesions were suspected on non-invasive imaging, coronary angiography was considered at that time. Some patients who attended our hospital late after the acute KD episode were also included. Those patients did not undergo coronary angiography immediately after the acute phase.

RESULTS

We found 17 lesions in 15 patients that were coronary dilatations developing late after KD (3%, 11 boys, four girls). All 15 had received anticoagulant treatment. Eight patients underwent coronary artery bypass grafting (CABG), and one patient underwent percutaneous balloon angioplasty. Late coronary artery dilatations after KD can be divided into two groups: new aneurysms and expanding aneurysms.

New aneurysms

We found 15 new aneurysms in 13 patients in the coronary arteries as follows: right coronary artery (RCA), three; left anterior descending coronary artery (LAD), eight; left circumflex artery, three; and left main trunk, one. Fourteen of 15 new aneurysms were in the proximal vessel segments. In 10 lesions, there had been a pre-existing aneurysm at the same site in the initial coronary angiography. Pre-existing aneurysms had been detected by echocardiography in the acute phase for three lesions. Acute stage status for the two remaining new aneurysms was unknown. The diameter of all pre-existing aneurysms exceeded 7 mm.

The age at onset of KD ranged from 3 months to 7.0 years (median 15 months). The interval from the onset of KD to the latest coronary angiography ranged from 4.4–22.1 years (median 12.5) and the time of first detection of new aneurysms ranged from 1.9–19.2 years (median 11.4 years) (table 1). The interval from the onset of KD to the first

Abbreviations: CABG, coronary artery bypass grafting; KD, Kawasaki disease; LAD, left anterior descending coronary artery; RCA, right coronary artery

Table 1 Characteristics of the new aneurysms

Age (years)	Sex	Interval from KD (months)	Segment	Diameter (mm)	LS (%)	Pre-existing aneurysm	Branching or bifurcation location	Eccentric
1.9	M	1.5	LCX 15	4.1	90	Yes	Branch	No
4	M	3.7	LAD 6	2.0	75	Yes	Branch	Yes
7	F	6.2	RCA 2	3.0	90	Yes	Branch	Yes
10	F	9.8	LAD 6	5.2	90	Yes	Branch	Yes
11	M	4.4	RCA 1	4.2	75	Yes	Branch	Yes
12	F	10.2	LAD 6	4.7	90	Yes	Branch	Yes
5	M	4.3	LMT 5	3.8	75	Yes	No	No
14	M	13	LAD 6	4.4	50	Yes	Branch	Yes
14	M	13	RCA 1	4.9	75	Yes	Branch	Yes
12	M	12	LAD 6	6.5	50	Unknown	Branch	Yes
17	F	16	LCX 11	2.5	25	Yes	Branch	Yes
17	F	13	LAD 6	5.4	25	Yes	Branch	Yes
7	M	6.2	LAD 6	5.1	50	Yes	Bifurcation	Yes
11	M	9.9	LCX 13	3.2	90	Unknown	Bifurcation	Yes
19	M	15.8	LAD 6	5.6	25	Yes	Bifurcation	Yes

F, female; KD, Kawasaki disease; LAD, left anterior descending coronary artery; LCX, left circumflex artery; LMT, left main trunk; LS, localised stenosis; M, male; RCA, right coronary artery

detection ranged from 1.6–16.3 years (median 9.9 years). The time of the first appearance of localised stenosis ⩾ 25% ranged from 1.0–16.3 years (median 5.4 years). In five lesions a new aneurysm and localised stenosis first appeared at the same time. For the remaining eight lesions the interval from the first appearance of localised stenosis to the appearance of new aneurysms ranged from 0.6–6.4 years (median 3.3 years).

The diameter of the new aneurysms ranged from 2.0–6.5 mm (median 4.4 mm). In nine of 11 lesions on follow up coronary angiography, the diameter of the new aneurysms was slightly increased, the increase ranging from 0.4–2.3 mm. After CABG, one new aneurysm with a diameter of 2.0 mm resolved, whereas the diameter of the other new aneurysm decreased slightly.

All new aneurysms had associated localised stenosis. The degree of stenosis was 25% in three patients, 50% in three, 75% in four, and 90% in five. Twelve lesions were post-stenotic and three pre-stenotic (table 1). A new aneurysm at the bifurcation or in the branches was seen in 14 patients (93%) (fig 1). In this study, branches referred to the small branching vessels from the major branches. Bifurcation referred to the bifurcation between the LAD and the diagonal branch or the bifurcation between the posterolateral and posterodescending branch. Thirteen new aneurysms were eccentric. None of the new aneurysms caused cardiac events, although the coronary artery of some patients was revascularised.

Three cases of new aneurysms

One girl developed KD when 4 months old. Giant aneurysms were seen on the RCA and the left coronary artery by two dimensional echocardiography. At coronary angiography four months after the onset the left coronary artery the aneurysm was smaller. An angiogram recorded seven years after the onset showed a 50% localised stenosis in the LAD and occlusion of the RCA (fig 2). She had not experienced chest pain. Ten years after the onset there was a new aneurysm with associated 90% localised stenosis in the LAD. The pressure gradient estimated by the velocity at the localised stenosis by two dimensional echocardiography was 31 mm Hg (fig 3). She underwent a CABG to the LAD. One year later the estimated pressure gradient was 4 mm Hg at the same lesion. The diameter of the new aneurysm decreased from 5.2 to 4.5 mm.

A boy had KD at the age of 15 months. Although he had severe heart failure he did not undergo coronary angiography at the time. An angiogram five years after the acute episode showed segmental stenosis in the RCA. Twelve years after the onset there was a new aneurysm with associated 50% localised stenosis in the LAD. Seven years later the findings were almost the same, although the aneurysm was slightly larger (fig 4). Figure 5 shows the intravascular ultrasound findings in the new aneurysm. In the proximal portion of the aneurysm intimal thickening was severe, in the aneurysm itself it was slight, and distally eccentric intimal thickening was detected.

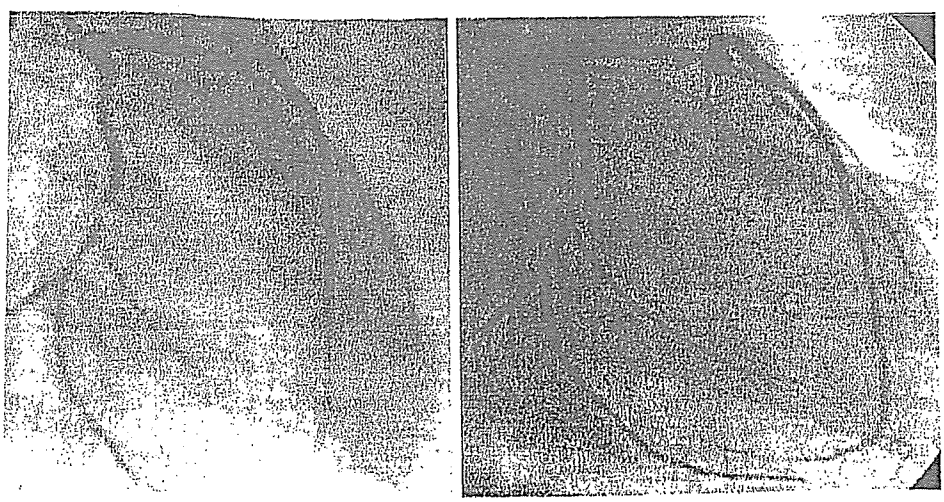

Figure 1 New aneurysm at bifurcation. Angiograms at (left) 8 years and (right) 7 years.

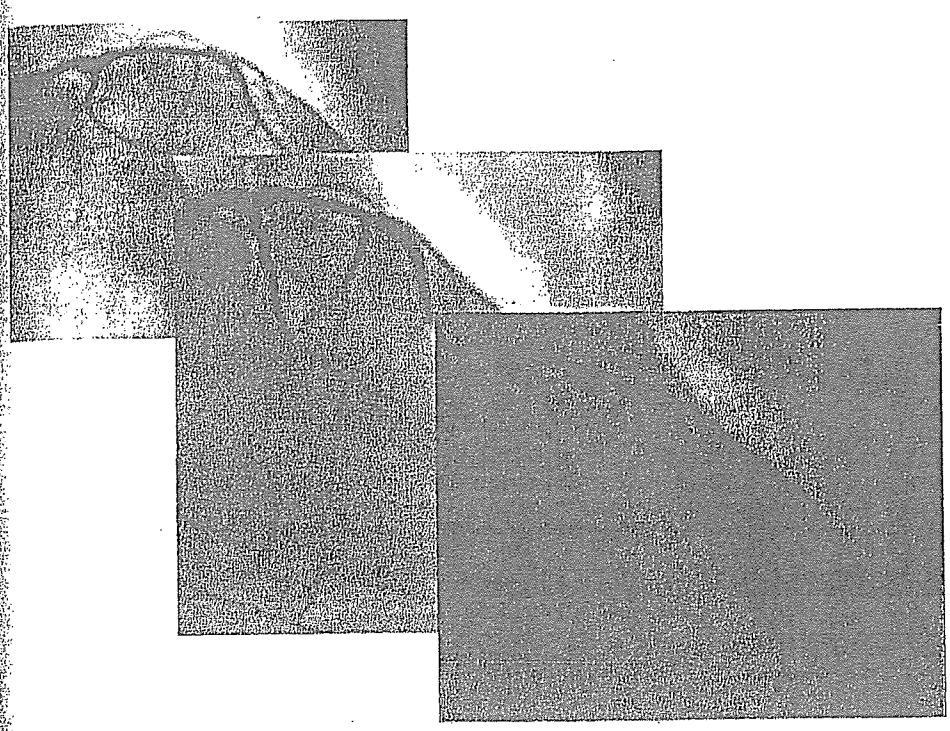

Figure 2 New aneurysm with severe localised stenosis that developed as a post-stenotic dilatation. Angiograms at (top) 2 years, (middle) 7 years, and (bottom) 10 years. The angiogram showed a new aneurysm with severe localised stenosis.

Another boy had KD at the age of 5 months. Two months after the onset angiograms showed aneurysms of the RCA and the LAD. Nine years after the acute illness an angiogram showed a 50% localised stenosis in the RCA. At 14 years there was a new aneurysm with 75% localised stenosis in the RCA and a new aneurysm with 25% localised stenosis in the LAD (fig 6).

Expanding aneurysms

Two expanding aneurysms were found, one in segment 1 of the RCA and the other in segment 6 of the LAD. One aneurysm of the RCA had decreased from 7.8 mm to 4.4 mm a year after its onset but subsequently enlarged to 19.5 mm over the next 17 years (fig 7). The other patient with an expanding aneurysm had KD when 11 years old. The

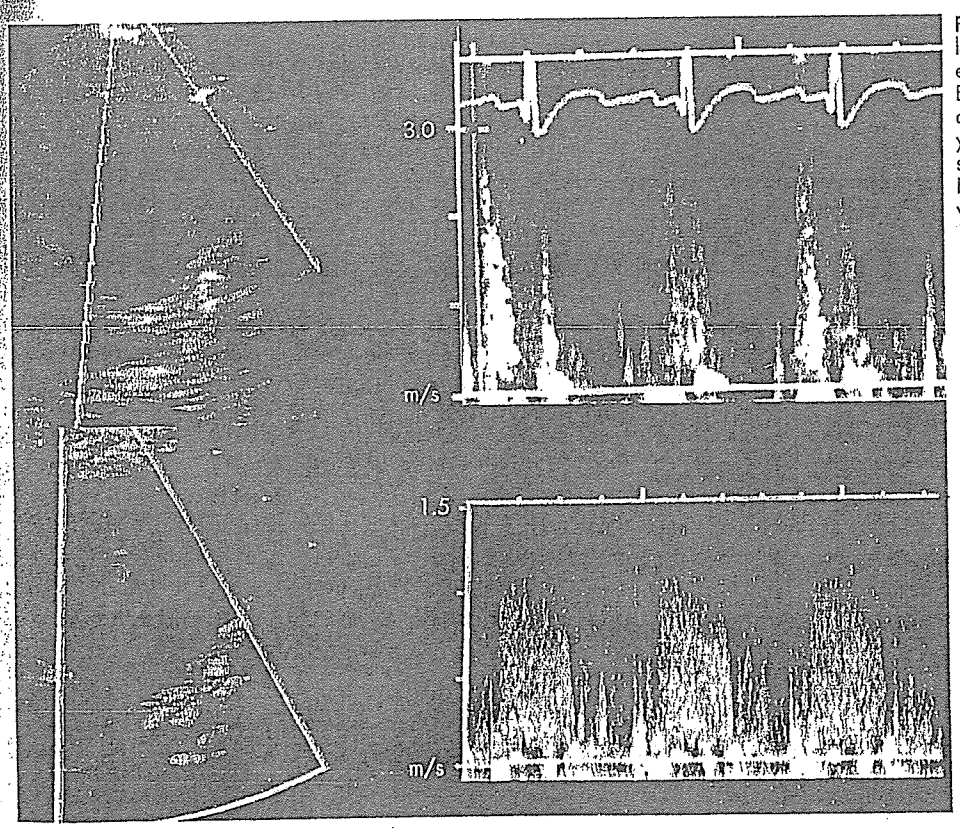

Figure 3 Pressure gradient at localised stenosis estimated by Doppler echocardiography. (Top) Echocardiogram before coronary artery bypass grafting (CABG) at 10 years. The velocity at the localised stenosis was 2.8 m/s. (Bottom) Echocardiogram after CABG. The velocity at the localised stenosis was 1.0 m/s.

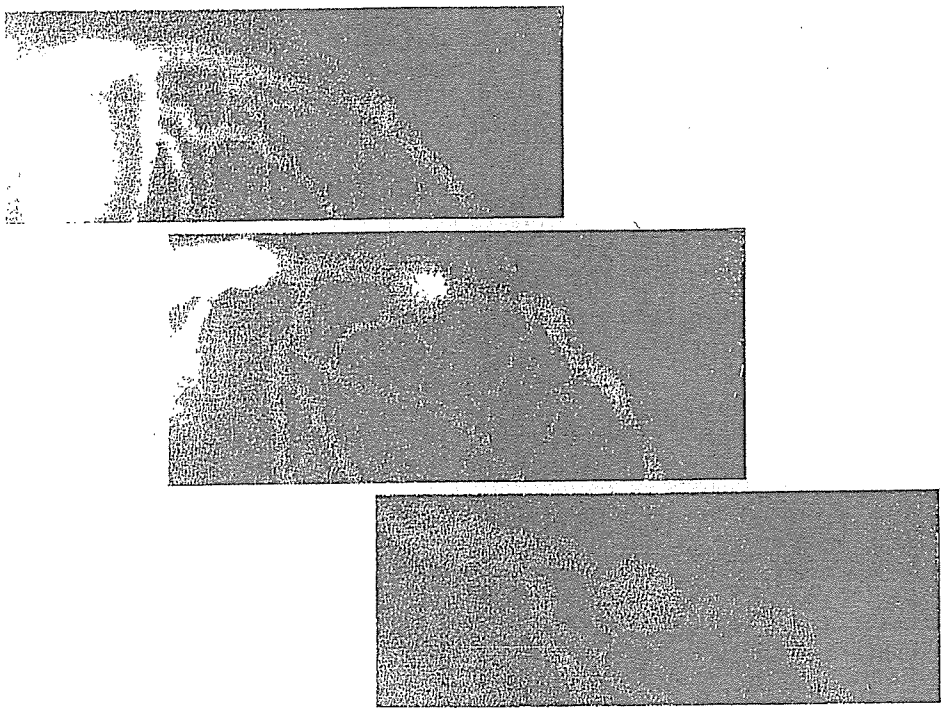

Figure 4 New aneurysm related to branching portion. Angiograms at (top) 5 years, (middle) 2 years, and (bottom) 19 years.

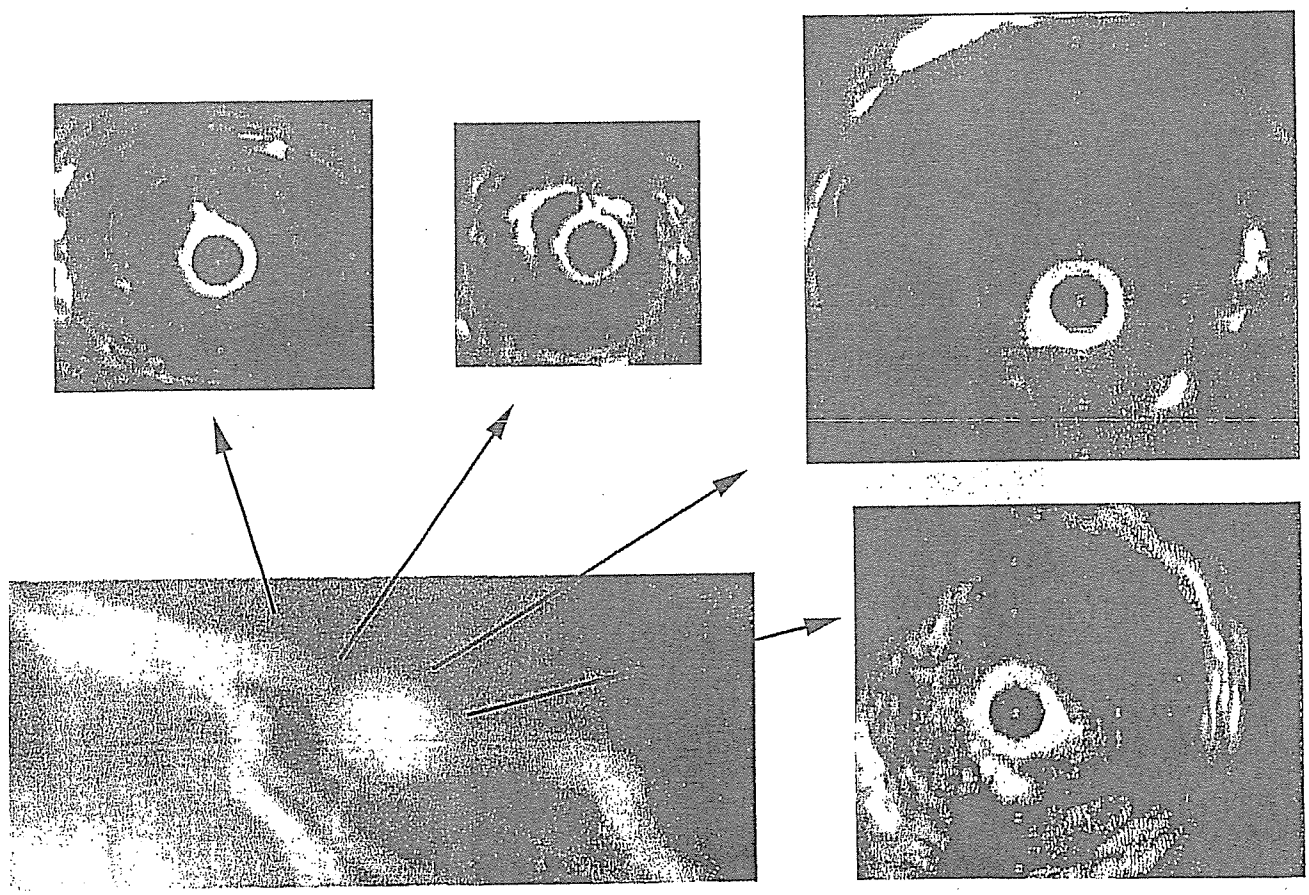

Figure 5 Intravascular ultrasound findings of a new aneurysm.

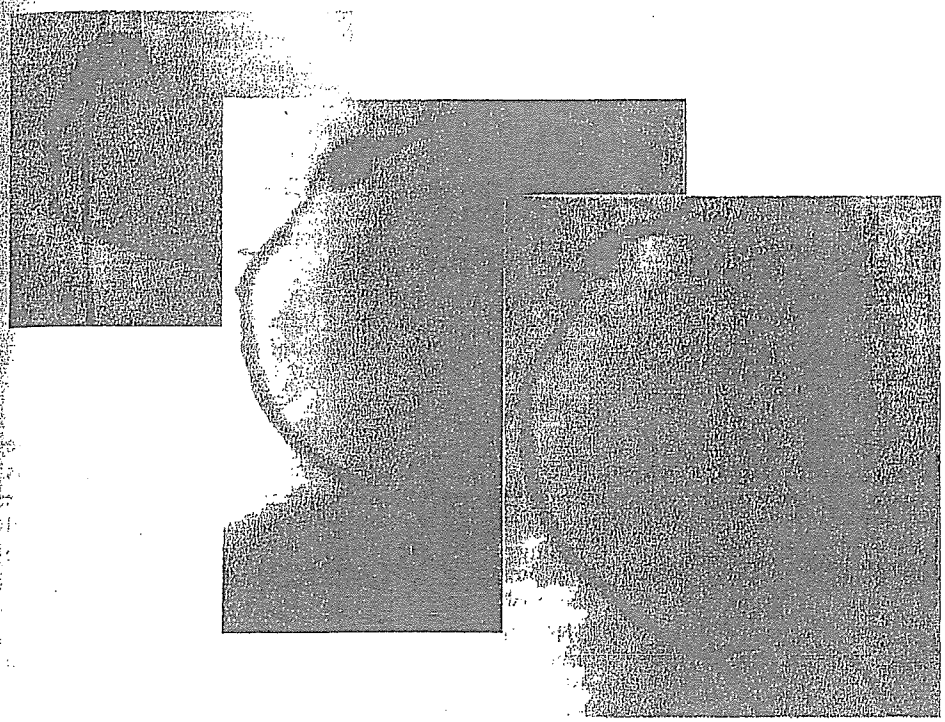

Figure 6 New aneurysm that developed as a pre-stenotic dilatation. Angiograms (top) two months, (middle) nine years, and (bottom) 14 years after onset.

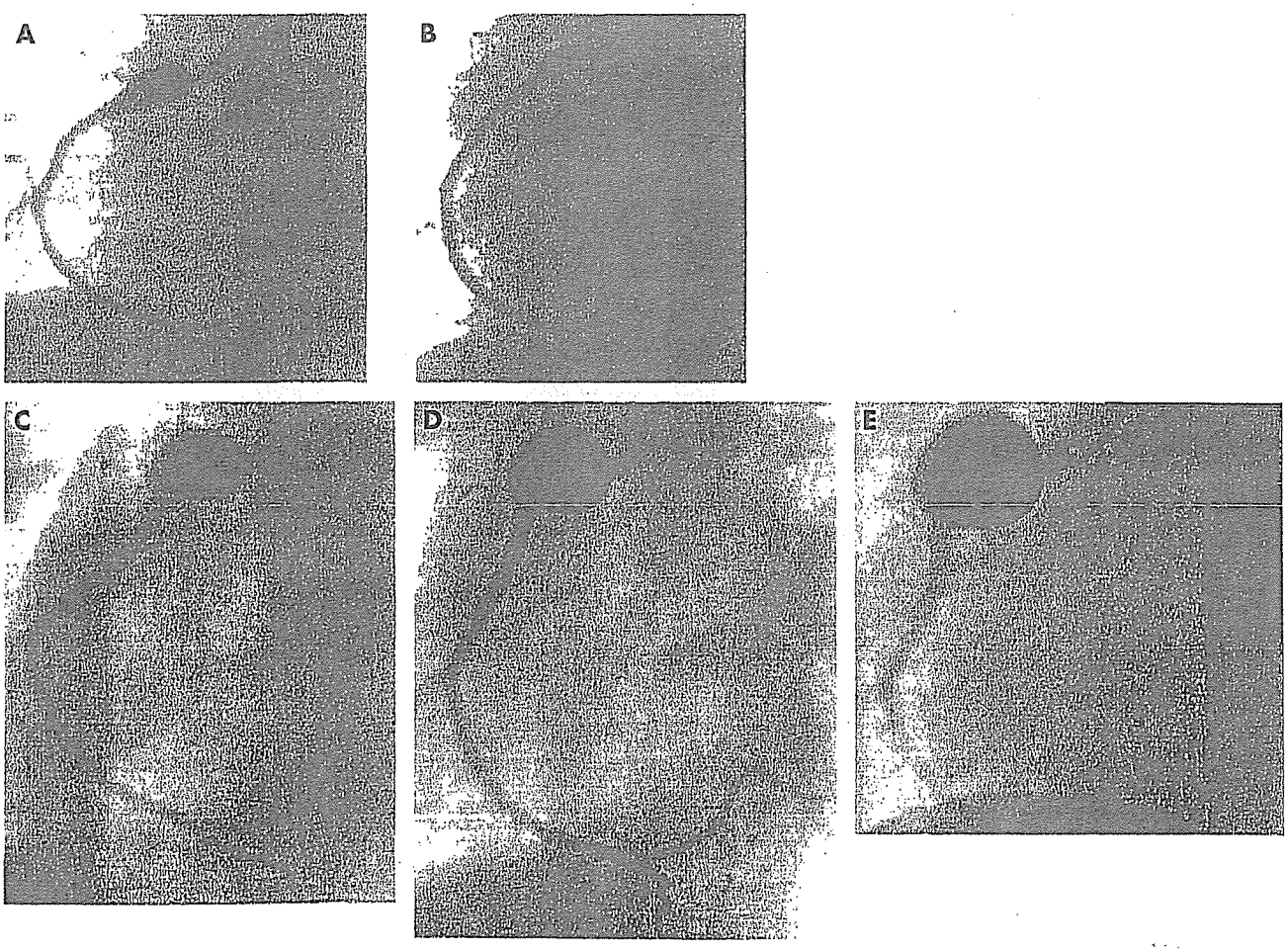

Figure 7 Angiographic follow up of an expanding aneurysm in a patient who had Kawasaki disease at the age of 18 months. Angiograms at (A) age 22 months (aneurysm diameter 7.8 mm), (B) 2 years 9 months (4.4 mm), (C) 10 years (9.6 mm), (D) 14 years (16.3 mm), and (E) 20 years (19.5 mm).

aneurysm increased from 10 mm to 15 mm in one year. Localised stenosis was not present in the two cases of expanding aneurysms and both patients were asymptomatic.

DISCUSSION

We found that new aneurysms developed in the same location at which there had been a pre-existing aneurysm. New aneurysms were aneurysms that redeveloped after previous regression. All pre-existing aneurysms were large and we hypothesised that the structure of the coronary arterial wall was irreversibly damaged by the severe acute inflammation. Most new aneurysms were associated with the appearance of severe localised stenosis. The pressure gradient generated by severe localised stenosis causes abnormal blood flow profiles, and these haemodynamic abnormalities exacerbate the existing damage from severe vasculitis. New aneurysms related to severe localised stenosis may be caused by pre-stenotic or post-stenotic dilatation. Furthermore, haemodynamic factors at the bifurcation and branches may predispose patients without severe localised stenosis to irregularity of the coronary wall. The wall properties at the bifurcation and branches may also favour aneurysm formation, as histologically the wall at a branching point is different from walls in other locations.[12]

Usually, the remodelling of localised stenosis after a large aneurysm caused by KD comprises severe intimal thickening.[5–8] It was thought that the coronary arterial wall of localised stenosis consisted of intimal thickening after regression of a large aneurysm; however, in this study the coronary arterial wall abnormalities late after KD were not only stenosis but also dilatation of the vessels, although such development was rare. Dilated coronary arterial lesions in the late period after KD indicated that the coronary arterial wall was irregular late after acute vasculitis. Although the cause is unknown, a small, weak portion in the thickened and firm wall may develop in the damaged coronary arterial wall after severe vasculitis caused by KD. The weak portion may be related to branching and may be dilated by the haemodynamic force of severe localised stenosis.

As most new aneurysms first appear during adolescence, growth of the coronary artery in relation to rapid somatic growth may also be a factor in causing new aneurysms. We must realise that the abnormality of the coronary arterial wall after regression of a large aneurysm consists not only of a thickened and firm portion but also a portion of partial thinning and weakness. This finding is useful for percutaneous coronary intervention, CABG, and long term follow up of patients with a history of a large aneurysm caused by KD.

Similarly, we believe that abnormalities of the coronary arterial wall contribute to the development of expanding aneurysms. Expanding aneurysms are proximal and subject to similar strong haemodynamic forces as is the aorta.[13]

The prevalence of dilated lesions in adult atherosclerosis and the occurrence of new aneurysms in cerebral aneurysms have been reported with a suggested incidence of 0.3–4.7%.[13–18] Haemodynamic factors, including hypertension, bifurcation wall characteristics, and weakening of the wall by atherosclerosis, were cited as causes. Some of these factors may also be common to the dilated coronary arterial lesions late after acute KD.

All new aneurysms were small or of medium size and, in our experience, neither new nor expanding aneurysms have led to clinical events. However, a patient with a new aneurysm and severe localised stenosis leading to occlusion has been reported on, although he remained asymptomatic.[11] The occurrence of cardiac events depends on the degree of localised stenosis. On the other hand, if a new aneurysm occurs in some cases, the progression of localised stenosis must be anticipated. A patient with an expanding aneurysm who was operated on to prevent rupture has also been reported on.[12] Acute myocardial infarction secondary to a large aneurysm certainly is possible. Such patients must be followed up closely and be given anticoagulants.

We emphasise the abnormalities of the coronary arterial wall in the appearance of new aneurysms. Therefore, although some of the new aneurysms were small, we called them "aneurysms" in this study on the basis of their shape. We must not ignore the abnormality of the coronary wall after apparent regression of a large aneurysm to prevent cardiac events in the future. Furthermore, we must develop a better understanding of long term changes in the vascular wall after severe acute vasculitis of KD.

Conclusion

New aneurysms and expanding aneurysms imply that the coronary arterial wall is abnormal late after previous regression. We suspect that new and expanding aneurysms result from haemodynamic factors in addition to partial weakening of the coronary wall late after acute severe vasculitis.

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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.

Keywords 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, 6, 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 ≥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 (Siemence Ancor Version 2.3.1). Measurements by each observer and between observers were reproducible with high correlation coefficients, as previously published [23].

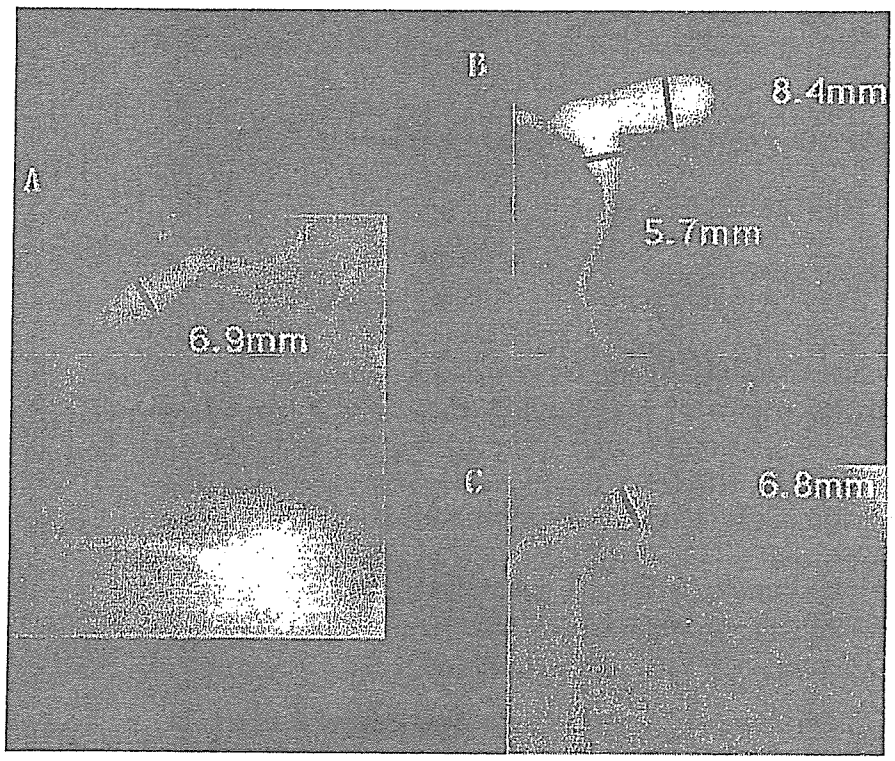


Figure 1 Measurement of coronary arterial diameter in the initial angiogram. (**A**) Right coronary artery. (**B**) Left anterior descending artery and left circumflex artery. (**C**) Bifurcation lesion of the left coronary artery.

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 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%.

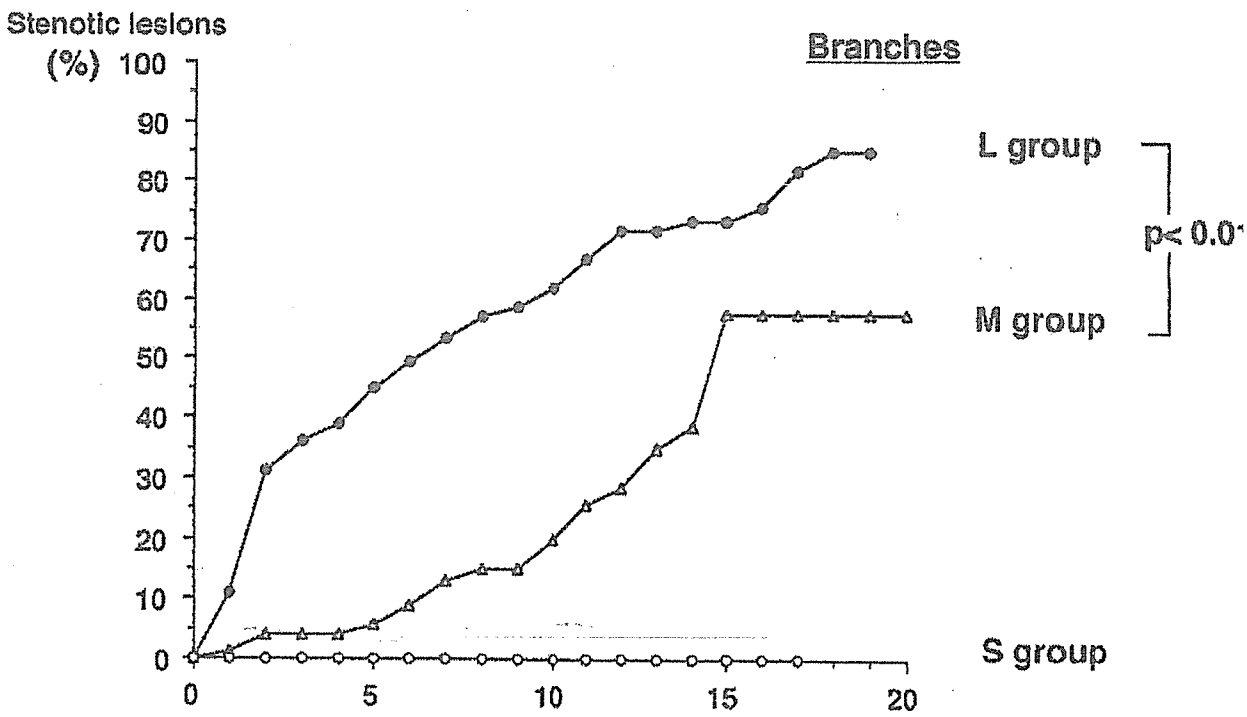
Table 1 Groups based on coronary artery diameter in the acute phase

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.

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.



years

Figure 2 Incidence of coronary stenotic lesions bated on coronary diameter in the acute phase (branches).

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 ($p < 0.01$).

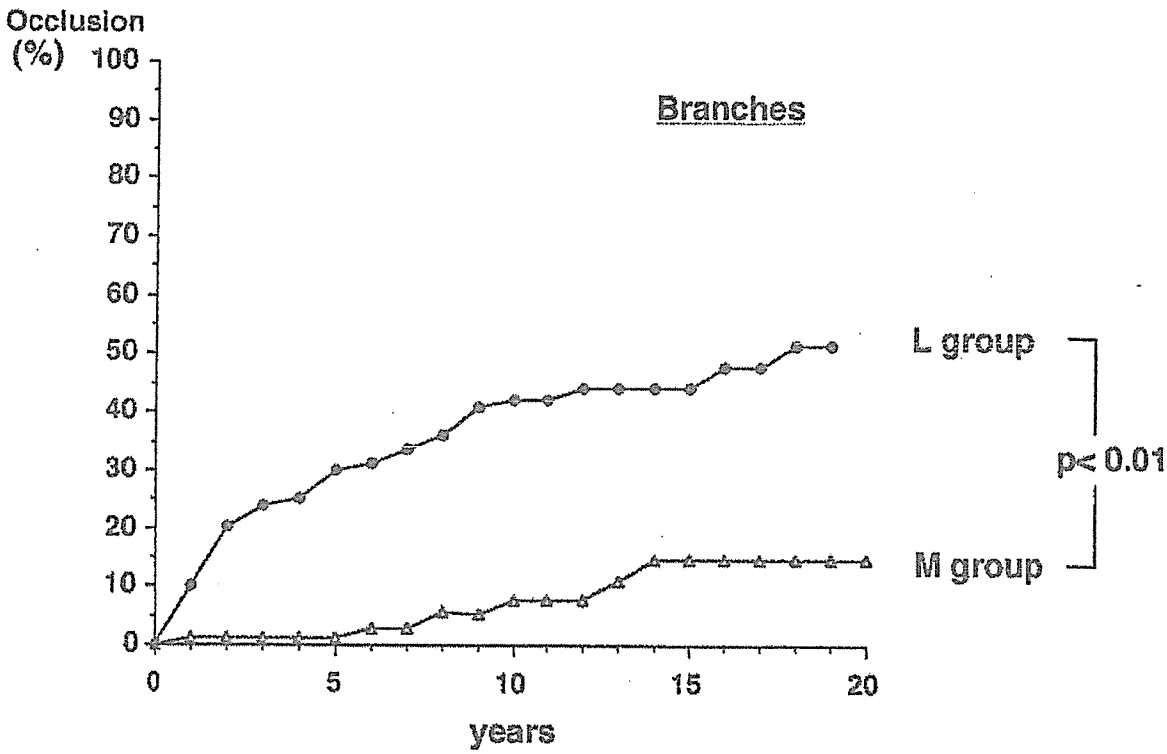


Figure 3 Incidence of coronary arterial occlusion based on coronary diameter in the acute phase (branches).

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

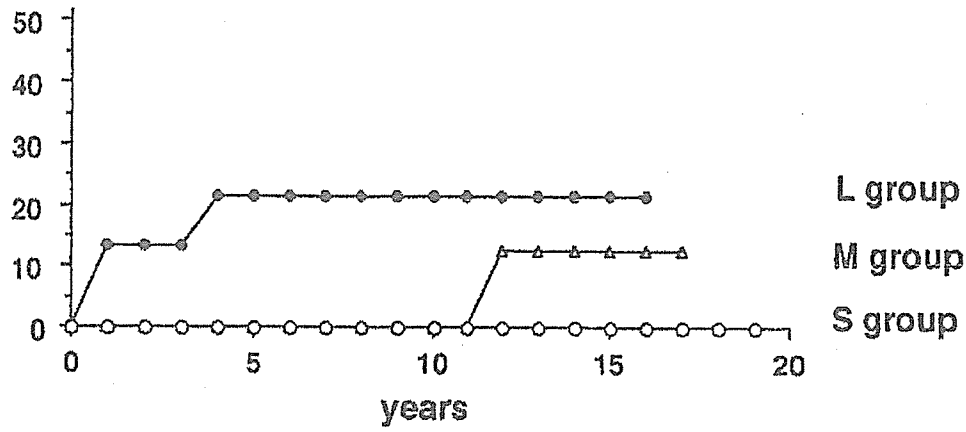


Figure 4 Incidence of coronary stenotic lesions based on coronary diameter in the acute phase (bifurcation lesions).

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 ($p < 0.01$).

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

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

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

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.

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

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 intima-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, measurement 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 fate 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 indicates a high probability of irreversible change in the coronary arterial wall, leading to subsequent stenosis or occlusion.

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