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Functional Behavior and Morphology of the Coronary Artery Wall in Patients With Kawasaki Disease Assessed by Intravascular Ultrasound

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Objectives. **To examine the development of coronary artery lesions in Kawasaki disease, we assessed the functional behavior and morphology of coronary arteries by intravascular ultrasound.**

Background. **Long-term follow-up studies of patients with Kawasaki disease have demonstrated the development of localized coronary stenoses even after aneurysms have regressed. It is also possible that angiographically normal coronary segments in patients with this disease may retain histologic changes.**

Methods. **Twenty-three patients followed up by serial coronary angiography were examined at a mean age ± SD of 14.9 ± 2.9 years. The thickness of the intima-media complex was measured by intravascular ultrasound (30 MHz; 3.5 or 4.3F; 1,800 rpm). Coronary reactivity to nitroglycerin was determined by measuring percent changes in cross-sectional coronary artery area after intracoronary injection (7 μg/kg body weight) of this agent.**

Results. **A remarkably thickened intima-media complex was observed at the sites with persisting (0.54 ± 0.20 mm, n = 19) and regressed (0.84 ± 0.40 mm, n = 23) aneurysms. Mild thickening of the intima-media complex was often observed even in angiographically normal segments (0.22 ± 0.05 mm, n = 31), in the left main coronary artery (0.47 ± 0.15 mm, n = 20) and at normal branches (0.36 ± 0.09 mm, n = 13). Coronary reactivity to nitroglycerin was significantly lower at the sites of regressed aneurysms (12.8 ± 6.6%, n = 9) than in normal segments (32.8 ± 10.9%, n = 13, p < 0.01), indicating the presence of functional impairment at the sites with regressed aneurysms. Decreased nitroglycerin reactivity was also observed in some segments without evidence of aneurysm.**

Conclusions. **These results indicate that in patients with Kawasaki disease the coronary disease accompanying impaired reactivity to nitroglycerin is present at the sites of regressed aneurysms as well as in angiographically normal coronary segments. We suggest that these sites with morphologic and functional abnormalities are related to the development of significant stenosis.**

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During the clinical course of Kawasaki disease, which is frequently associated with the development of coronary artery aneurysms in the acute phase, a progressive localized stenosis may appear at the sites of aneurysms (1). In addition, apparently normal coronary arteries have been reported to retain histologic abnormalities, and the possibility of a higher incidence of eventual arteriosclerosis in patients with Kawasaki disease (2) has been of great concern (3–5).

Most coronary artery aneurysms associated with Kawasaki disease decrease in size relatively soon after the acute phase of that disease. This condition of aneurysm regression, defined as the complete disappearance of aneurysms on angiography (6), has been reported (1,6) to occur in ~30% to ~60% of patients. This angiographic normalization of the coronary arteries has been considered an indication of satisfactory progress and the likelihood of a good outcome. However, a long-term follow-up study of coronary lesions (1) in patients with Kawasaki disease demonstrated the occurrence of progressive localized stenosis >10 years after aneurysm regression.

According to the histologic studies (2), even an apparently normal coronary artery with no history of dilated lesions associated with aneurysms could have some degree of intimal thickening, suggesting a relation between the appearance of the stenotic lesion late after Kawasaki disease and the presence of thickened intima. However, few data exist regarding the relation between coronary artery morphology and function and the development of stenosis in Kawasaki disease. In the present study, we used intravascular ultrasound imaging to assess the potential for development of stenotic lesions after Kawasaki disease, the morphology of the coronary arteries and their vasoreactivity to nitroglycerin.

Methods

Study subjects. The research protocol was approved by the Hospital Medical Ethics Committee of the National Cardio-

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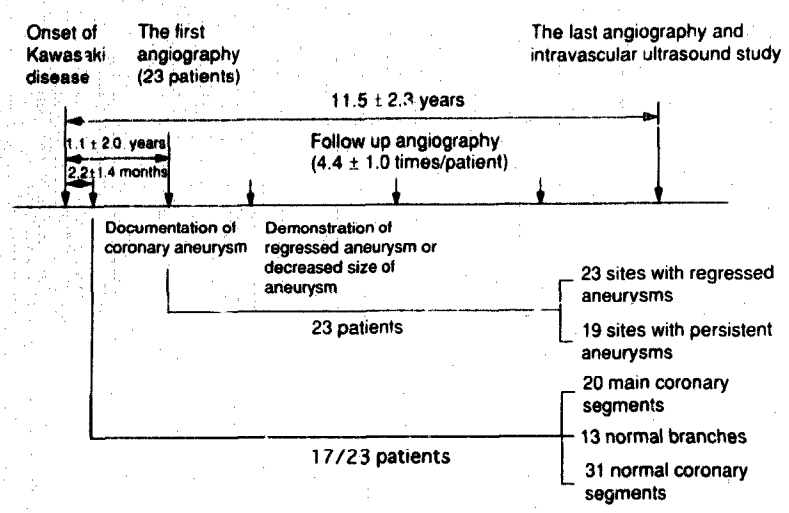

Figure 1. Diagrammatic representation of the study protocol.

vascular Center of Japan (no. 05-3, 1993) and written informed consent was obtained from all patients.

Twenty-three patients with coronary artery lesions associated with Kawasaki disease were examined with intravascular ultrasound. Their mean age ± SD at the onset of Kawasaki disease was 3.3 ± 2.3 years, and they were subsequently followed up for 11.5 ± 2.3 years (Fig. 1). Coronary angiography was performed during the follow-up period an average of 4.4 ± 1.0 times/patient. All 23 patients were noted to have coronary aneurysms on their first coronary angiographic study, which was performed a mean of 1.1 ± 2.0 years after the onset of Kawasaki disease. Normal coronary sites without lesion involvement were analyzed in 17 of the 23 patients, who underwent their first angiogram within 6 months (mean 2.2 ± 1.4 months) from the onset of Kawasaki disease. The six patients who first underwent angiography >6 months after onset of Kawasaki disease were excluded from the study of normal coronary sites, because the aneurysmal sites that showed regression early (within 6 months) after the onset of the disease could be misinterpreted as normal sites (Fig. 1).

The intravascular ultrasound studies were obtained at the time of the patients' last coronary angiographic study, performed when the patients were 8.8 to 21.2 years old (mean 14.9 ± 2.9). In all patients, the previous angiographic study had confirmed complete regression or decreased size of the coronary aneurysms. In two coronary sites, slight localized stenoses appeared in the previous angiographic study. During the follow-up period, all 23 patients showed normal serum levels of total cholesterol, triglyceride and high-density lipoprotein cholesterol as determined by standard methods at least once a year.

Ultrasound imaging of coronary wall. The intravascular ultrasound images were obtained by using the mechanically rotating ultrasound imaging system with an operating frequency of 30 MHz (4.3F; 1,800 rpm, Cardiovascular Imaging System Inc, or 3.5F, 1,800 rpm, Boston Scientific Corporation). All images were continuously recorded on S-VHS videotape and were digitized into 640 × 480 pixel matrices for subsequent data analysis.

Thickness of the intima-media complex was measured with an electric cursor as a distance between the lumen–vessel wall interface and the trailing edge of the echolucent zone in the ultrasound images. The lumen cross-sectional area of the coronary arteries was measured by tracing the lumen–vessel wall interface. At this time, injection of a small amount of contrast medium was quite helpful in recognizing the border between the lumen and the intimal leading edge.

Studied coronary segments. Vascular wall morphology was evaluated at several sites (Fig. 1). 1) Sites of persisting aneurysms with decreasing size (on 19 coronary branches) and of regressed aneurysms (on 23 coronary branches). The remaining examinations were performed at the sites of angiographically normal coronary arteries, including normal segments on 31 coronary branches, 20 sites in both main coronary arteries and 13 sites in branches of normal coronary arteries. At each observation site, the intima-media complex with the maximal thickness was selected for the analysis.

Evaluation of nitroglycerin reactivity. The vasoreactivity of the coronary arteries to nitroglycerin was assessed in 22 of the 23 study patients (we excluded 1 patient who received a long-acting calcium antagonist that might affect the reactivity to nitroglycerin). No vasodilator was given before this examination in these 22 patients. Among them, the intravascular ultrasound catheter was initially placed at the sites of regressed aneurysms in 9 patients; in the other 13 patients the intravascular ultrasound studies were performed at the sites of the normal coronary segments in the first angiographic study.

A bolus of nitroglycerin, 7 μg/kg body weight, was administered into the coronary artery through the 7F guiding catheter (Superflow, Schneider). The intravascular ultrasound im-

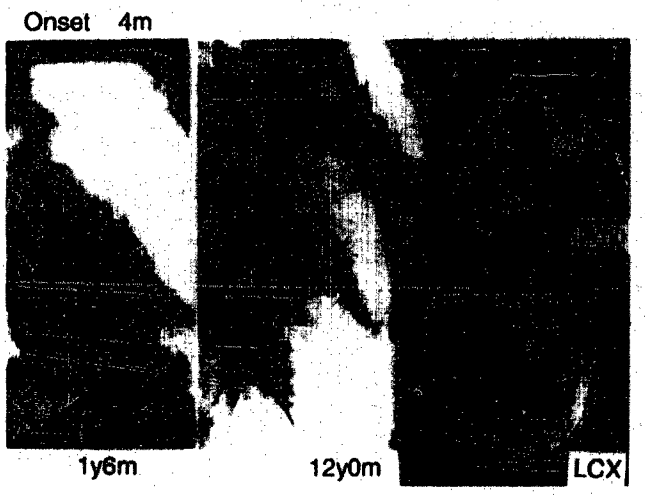

Figure 2. Case 1 (onset of Kawasaki disease at age 4 months [4 m]). The first coronary angiogram **(left panel)** was obtained at age 1 year 6 months (1 y 6 m) and the latest examination **(center panel)** at age 12 years (12 y 0 m). On intravascular ultrasound images **(right panels)**, a persisting aneurysm in the left circumflex artery (LCX) showed a mildly thickened intima-media complex at the site of the regressed aneurysm. In the left anterior descending artery (LAD), remarkable intimal thickening with calcification had induced significant narrowing of the vessel lumen.

age was continuously monitored and recorded for ≥60 s after nitroglycerin administration (7). The lumen area was measured before nitroglycerin administration to obtain a baseline value and every 2 s after administration. Then, the frame at the point of maximal vessel dilation was selected for the measurement of percent changes in lumen area from baseline. At the sites of the regressed aneurysm, we also studied the relation between the ratio of vasodilating response and the index of intimal thickening, which was calculated as [(Lumen area + Intima-Media area) − Lumen area]/(Lumen area + Intima-Media area) × 100 (%). All measurements were performed in blinded manner by two investigators (A.S., H.S.) working independently.

Intraobserver and interobserver variability. Thickness of the intima-media complex and cross-sectional areas of 10 randomly selected sites were measured by two independent observers and by one observer at two separate times. These data were used to assess interobserver and intraobserver variability. The result was expressed as a linear regression between the two measurements and as a percent error that was derived as the absolute difference between measurements divided by the initial measurements.

Statistics. All data are expressed as mean value ± SD. All simple group comparisons were made by using an unpaired or paired Student *t* test. The relation between nitroglycerin reactivity and the index of intimal thickening and interobserver and intraobserver variabililties were determined by simple regression analysis. We considered differences significant at a p value < 0.05.

Results

Observer variabilities. Interobserver variability for measurement of the thickness of the intima-media complex (standard deviation) was ±4.0% with a correlation coefficient of r = 0.987; intraobserver variability was ±2.5% (r = 0.996). Respective data for measurement of cross-sectional area were 0.6% (r = 0.999) and ±1.6% (r = 0.998).

Assessment of coronary artery wall morphology. The intima-media complex at sites with persistent aneurysms ranged from 0.26 to 0.89 mm (mean 0.54 ± 0.20) (Fig. 2), that at sites with regressed aneurysms ranged from 0.28 to 1.97 mm (mean 0.84 ± 0.40) (Fig. 2 to 4). A three-layer appearance of the coronary artery wall was observed at some portions even in the absence of angiographic disease. The intima-media complex of

Figure 3. Case 2 (onset of Kawasaki disease at age 7 months [7 m]). The first coronary angiogram **(left panel)** was obtained 1 month after the onset of Kawasaki disease and the latest examination **(top right panel)** at age 11 years 11 months (11 y 11 m). At the site of the regressed aneurysm in the left anterior descending artery **(a)**, the angiographic findings were apparently normal, but on the intravascular ultrasound images **(right inset)**, this site showed remarkable thickening of the intima-media complex and calcification; the regressed aneurysm in the left circumflex artery **(b)** also showed remarkable intimal thickening.

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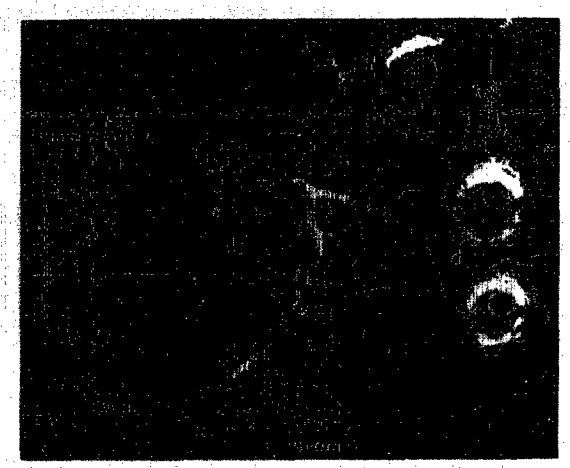

Figure 4. Case 3 (onset of Kawasaki disease at age 5 years 1 month [5 y 1 m]). The first angiogram (**left panel**) was obtained 1 month after the onset of Kawasaki disease and the latest examination (**center panel**) was performed at age 19 years (19 y 0 m). The initial angiogram showed no left main coronary artery lesion, but intravascular ultrasound imaging (**top** and **right panels**) showed mild but significant intimal thickening in this segment (**a**) and moderate thickness of the intima-media complex (**b**) at the site of the regressed aneurysm. Although the distal portions of the left anterior descending artery had remained normal since the first angiogram, the intravascular ultrasound images showed mild thickening of the intima-media complex in these segments (**c, d**).

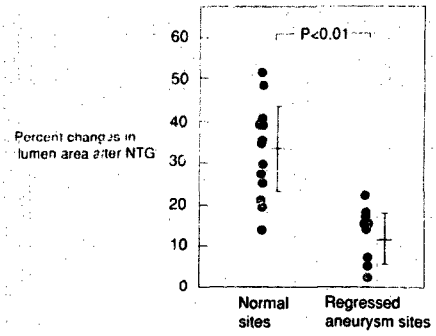

Figure 5. Comparison of nitroglycerin (NTG) reactivity at the angiographically normal sites and the sites of the regressed aneurysm after Kawasaki disease.

these normal segments ranged from 0.16 to 0.37 mm (mean 0.22 ± 0.05) (Fig. 4). The intima-media complex of angiographically normal left main coronary arteries (Fig. 4) ranged from 0.16 to 0.79 mm (mean 0.47 ± 0.15), and at normal coronary artery branches it ranged from 0.25 to 0.58 mm (mean 0.36 ± 0.09). When thickness of the intima-media complex >0.30 mm was considered abnormal (8,9), abnormal sites were associated with 95% of persistent aneurysms, 96% of regressed aneurysms, 10% of normal segments, 85% of normal main coronary arteries and 85% of the normal branches.

Among the 23 sites of regressed aneurysms, localized stenosis was detected in 6 sites (26%), 2 of which had been detected on the preceding angiogram as a mild lumen irregularity. The remaining four stenoses were detected by intravascular ultrasound as significant localized lesions with remarkable calcification of intimal plaque (Fig. 2 and 3), although, by angiography, these were observed as newly developed minor irregularities or slight narrowing of the arterial wall.

Coronary artery calcification was observed at only two sites by angiography but at nine sites by intravascular ultrasound, including seven sites (30%) with a regressed aneurysm and two sites (11%) with a persistent aneurysmal wall. All of these calcifications were detected at the innermost lumen wall as the line of the very strong, bright echocardiographic signal with ultrasound shadowing. Under these conditions, it was unclear whether deep calcification was present, because deep sites were difficult to observe because of the occurrence of shadowing.

Coronary reactivity to nitroglycerin. Maximal coronary artery dilation was observed 45 ± 12 s after the intracoronary administration of nitroglycerin. The percent change in the cross-sectional area at the point of maximal dilation from the baseline in the 9 sites with aneurysm regression ranged from 2.3% to 22.0% (mean 12.8 ± 6.6%), and in the 13 sites with angiographically normal segments it ranged from 13.8% to 51.9% (mean 32.8 ± 10.9%, $p < 0.01$, Fig. 5). However, in some of the angiographically normal sites with relatively thin intima, the maximal reactivity to nitroglycerin was markedly impaired, suggesting the presence of functional abnormality even in the absence of coronary disease on both angiographic and ultrasound study. At the sites with aneurysm regression, there was a weak inverse correlation between the index of intimal thickening (range 4% to 49%) and the percent change in lumen area after nitroglycerin ($y = -0.27x + 17$, $r = 0.66$).

Discussion

Vessel wall morphology after Kawasaki disease. A previous intravascular ultrasound study regarding coronary artery lesions associated with Kawasaki disease (9) showed that the intimal surface within the regressed aneurysm was quite smooth, although the intimal thickness markedly increased. This observation suggests that the regression of aneurysms could be considered as part of the healing process after the acute stage of Kawasaki disease. However, as shown in the present study, some of the regressed aneurysms were accompanied not only by remarkable intimal thickening but also by narrowing of the lumen with or without calcification. Therefore, it is obvious that the regression of aneurysms does not necessarily indicate satisfactory healing of coronary lesions.

Some angiographically normal coronary segments that were without aneurysmal lesions during the acute phase of Kawasaki disease also showed a slight increase in thickness of the intima-media complex. According to previous studies (8,9)

using an almost identical ultrasound system, thickness of the intima of the normal coronary artery should be <0.235 mm with a mean of 0.161 mm in young adults. Also a three-layer appearance in the ultrasound image itself has been reported (10) to indicate the presence of abnormal thickening of the intima in young adults. However, in our study, a three-layer appearance with intimal thickness <0.30 mm was often observed even in apparently normal coronary arteries without angiographic evidence of aneurysmal involvement. Therefore, it is possible that the presence of a three-layer appearance with a thin intima does not necessarily indicate pathologic thickening of the vessel wall at the coronary segments examined in our study.

However, some of the coronary sites without angiographic lesions in both the acute and chronic phases of Kawasaki disease showed a localized increase in intimal thickness to >0.30 mm. These segments with mildly thickened intima were often seen at the main coronary arteries or at the branches in the normal portion of other coronary arteries. In a pathologic study in children (11), 2% to 6% of the subjects without any history of cardiovascular disease showed atherosclerotic lesions, mainly at branching points of the left coronary artery, at age 6 to 15 years. In contrast, the frequency of the presence of mildly thickened intima at the branches, main trunks and normal coronary segments in our study was extremely high (85%, 85%, 10%, respectively) compared with that in the pathologic study. This finding suggests that the intimal thickening observed in coronary arteries after the onset of Kawasaki disease may not be nonspecific atherosclerotic changes but lesions specifically induced by the disease.

Functional abnormalities of the diseased vessel. We (7) previously reported that the cross-sectional area of normal coronary segments increases by an average of 31% after the administration of nitroglycerin. Using angiography, Brown et al. (12) reported that vasodilation with nitroglycerin was 35% in normal vessels, 1.6 to 2.3 mm in diameter, corresponding to the sites of normal segments in our study. In the children we studied, the dilating capacity of the normal coronary arteries was presumably greater than that of the arteries of the elderly adults in these studies.

Despite the angiographically normal appearance, the coronary sites after regression of aneurysms showed significantly reduced vasodilating capacity (12.8% on average), and there was a tendency for an inverse correlation between the vasodilating capacity and the index of intimal thickening. These data suggest that, in addition to structural changes of the media during the clinical course of Kawasaki disease (13), vasoreactivity can be impaired at the sites of aneurysm regression in association with the development of the intimal thickening.

Some angiographically normal sites without evidence of previous aneurysmal changes also showed impaired vasodilatation after nitroglycerin. Previous reports concerning the vasodilator response induced by dipyridamole (14) or isosorbide dinitrate (15) demonstrated a significant decrease in the vasodilating capacity of the vessel at the sites of aneurysms (14) and at such sites after the aneurysms had regressed (15). We previously demonstrated that using intravascular ultrasound vasodilatation after nitroglycerin mainly occur in the relatively normal portion of the noncircumferential lesions, whereas the diseased portion remained unchanged. The present data indicate that the abnormal coronary reactivity to nitroglycerin involved not only the site of regressed aneurysms but also part of the angiographically normal coronary segments where dilated lesions had not been documented. It is possible that these structural and functional changes of the coronary artery after Kawasaki disease are related to the occurrence of further stenotic changes regardless of angiographic appearance of the coronary arteries.

Limitations of the study. Our study has several limitations. First, we employed angiographic criteria for aneurysm regression. Therefore, one might argue that the angiographic regression we observed was due to ectasia of the adjacent site during follow-up angiography. However, we confirmed that the apparent regression occurred within 1 year after the diagnosis of Kawasaki disease by serial angiography. Thus, we believe that the regression we observed was derived not from growth of the adjacent coronary sites but from the thickening of the vessel wall.

Second, we employed nitroglycerin, an endothelium-independent vasodilator, to assess coronary reactivity. One might suggest that another agent such as acetylcholine, which is an endothelium-dependent vasodilator, would be more sensitive in detecting vessel wall dysfunction (16) associated with inflammatory changes after Kawasaki disease. However, it is possible to speculate that from the results of nitroglycerin reactivity the coronary sites after Kawasaki disease could be involved by functional abnormality that may be related to the appearance of the stenotic lesions in the chronic phase of the disease.

It is unclear when, during the course of Kawasaki disease, the thickening of the intima at the sites with aneurysms occurred, because the intravascular ultrasound study was not performed during the acute phase of the disease owing to the technical problems of inserting the ultrasound transducer into small coronary arteries. With use of smaller ultrasound devices, it may be possible to observe intimal changes in the early phase of development of the aneurysm, which may aid in the prediction of the development of localized stenosis.

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