Intravascular Ultrasound of Coronary Arteries in Children
Assessment of the Wall Morphology and the Lumen After Kawasaki Disease

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Background The long-term clinical issue in Kawasaki disease (KD) concerns the coronary artery lesion. Two-dimensional echocardiography and coronary angiography are routine examinations to evaluate the coronary lesions; however, these are not adequate to assess the wall morphology of the coronary artery (CA). Intravascular ultrasound imaging (IVUS), a new technology for the evaluation of the coronary artery lumen and wall morphology in vivo, was performed for patients after KD in their long-term follow-up, and we examined the new insights it gave.

Methods and Results IVUS was performed during cardiac catheterization in 20 subjects (10 patients after KD who still had coronary aneurysms or regressed coronary aneurysms, 2 after KD who had no coronary abnormal lesion, and 8 control patients with congenital heart disease and normal CA). We evaluated the wall structure at 10 to 15 sites of the CA in each patient. IVUS was performed with a commercially available ultrasound imaging catheter. Four sites of a CA aneurysm in KD demonstrated a markedly dilated lumen without thickened intima. One site of a CA aneurysm with calcification demonstrated an asymmetrical lumen by a dense echo with acoustic shadows. Twenty-two sites of a regressed CA aneurysm demonstrated a marked symmetrical or asymmetrical thickening of the intima with a dense echo, in which the size of the lumen was similar to that at a site near a regressed aneurysm. The sites of angiographically normal CA revealed normal structures and a thin intima in many instances. Nine of 28 sites in KD with a CA abnormal lesion, particularly near a coronary aneurysm or regressed aneurysm, demonstrated a mild thickening of the intima. All the 10 sites in KD without a CA abnormal lesion and all the 25 sites in patients with congenital heart disease with normal CA demonstrated a smooth intima.

Conclusions This study demonstrated that the site of a regressed coronary aneurysm has a markedly thickened but smooth intima. The sites of angiographically normal CA after KD with or without a coronary lesion demonstrated normal IVUS findings in most instances but in some cases revealed a mild intimai thickening. IVUS is useful to evaluate the CA wall morphology and may contribute to the assessment of long-term CA sequelae and the possible development of arteriosclerotic changes in KD. (Circulation. 1994;89:258-265.)

Key Words • Kawasaki disease • coronary aneurysm • arteriosclerosis • intravascular ultrasound • coronary angiography

Kawasaki disease (KD) is an acute febrile vasculitis that affects primarily infants and young children. During the acute stage of KD, coronary artery aneurysms develop in 10% to 20% of patients; this is the most serious complication, because coronary aneurysms may cause sudden death or ischemic heart disease as a result of thrombotic or stenotic occlusion of the coronary artery.1 We have reported that 60% of patients with a coronary aneurysm demonstrated regression of the aneurysm by follow-up coronary angiography within 1 or 2 years after the acute illness; however, the mechanism and outcome of the regression of the aneurysms are uncertain.2,3 The long-term clinical issue in KD concerns the coronary artery lesions, which involve aneurysm formation, thrombotic occlusion, progression to ischemic heart disease, and premature atherosclerosis. Two-dimensional echocardiography and selective coronary angiography are standard methods to evaluate coronary artery lesions; however, these are limited to assessment of wall morphology. Recent progress in intravascular ultrasonic technology now allows real-time tomographic imaging of the vascular structures and pathological lesions in vivo. Many reports of intravascular ultrasound imaging (IVUS) on the coronary artery in adults with and without ischemic heart disease have appeared recently.4-12 However, no data are available on IVUS on the coronary artery in KD and in children.

Methods

Patients

IVUS was performed during cardiac catheterization in 20 patients, including 12 patients in follow-up after KD and another 8 patients with congenital heart disease and normal coronary arteries. The patients’ profiles are shown in Table 1. Children after KD. The children after KD involved 8 boys and 2 girls who had had coronary aneurysms in the acute stage of the illness evaluated by both two-dimensional echocardiography...
raphy and selective coronary angiography. All these patients had been followed in our hospital and were receiving follow-up coronary angiography several years after the first study. The coronary aneurysms in the acute stage had regressed and changed to normal findings at the second angiography in 6 patients (5 boys and one girl), whereas the coronary aneurysms in the other four patients (3 boys and one girl) were unchanged at the second angiography. Two more children after KD who had no abnormal lesion in the coronary arteries evaluated by two-dimensional echocardiography in the acute stage of the illness underwent coronary angiography and IVUS in this study because they had complained of chest pain at 11 and 12 years, respectively, after acute KD. Both the follow-up angiography and IVUS found no abnormality in the coronary arteries. The ages of the 12 patients at the follow-up coronary angiography ranged from 8.8 to 15.0 years (mean, 11.6±2.1 years in patients with coronary aneurysms, 13.6±1.6 years in patients with no abnormal coronary lesion). The IVUS was performed during the follow-up coronary angiography. The coronary angiography demonstrated that 6 patients had regression of the aneurysms, whereas 4 patients showed persistent aneurysms, and 1 of these 4 patients developed coronary artery stenosis. The intervals from the onset of the illness to the time of the IVUS study ranged from 7.0 to 14.7 years (mean, 9.3±1.6 years).

All patients with KD had received treatment with aspirin (30 mg/kg per day in the acute phase and 5 mg/kg per day in the convalescent phase). No patient was given high-dose ɣ-globulin during the acute phase because our patients were affected by KD before this was recognized to be a standard treatment for acute KD. No patient with KD had any palpitation, arrhythmia, or myocardial infarction during our follow-up.

Control group. The control patients were eight children with congenital heart disease such as atrial septal defect, small patent ductus arteriosus, or small ventricular septal defect with no history of KD and normal coronary arteries. These were evaluated by IVUS during the diagnostic and intervention catheterization. They underwent selective coronary angiography, which showed normal coronary arteries, before IVUS. The mean age of the control group was 10.2±2.8 years.

The study protocol was approved by the Kurume University School of Medicine Ethics Committee, and informed consent was obtained from the parents of all the patients.

### Coronary Angiography

A 7F, 8F, or 9F sheath was inserted percutaneously into the femoral artery, and a 5F or 6F Judkins-Kato catheter (Cook Co, Bloomington, Ind) for pediatric coronary angiography was advanced through the sheath up to the ostium of the right or left coronary artery by the Judkins technique. We measured the systemic arterial pressure through the sheath and checked the heart rate by ECG monitoring. Cineangiography of the left and right coronary arteries was performed by manual injection of Iohexol into the right or left coronary artery through the Judkins-Kato coronary angiographic catheter under ECG monitoring. The right anterior oblique 30° projection, the posterior anterior projection, or the left anterior oblique 60° projection was taken for the coronary angiography. The cineangiography system was a model KXO-2050 (Toshiba Corp, Japan). After the coronary artery lesions were ascertained, IVUS was performed.

#### Intravascular Ultrasound Imaging

The sheath was placed in the femoral artery, and then a 7F or 8F right or left Judkins large-lumen guiding catheter with a 0.14-in angioplasty guide wire was advanced into the coronary ostium. After this guide wire was withdrawn, an ultrasound imaging catheter with a 30-MHz transducer (CVIS Inc, Sunnyvale, Calif) at its tip was advanced over another, finer (0.014-in) guide wire through the guiding catheter into the necessary coronary portion to record the coronary artery lesion. The size of the ultrasound imaging catheter was 4.3F or 5F. The intracoronary ultrasound image was displayed on a fluoroscope. The coronary arteries were imaged through the guiding catheter by angiography to determine the location of the tip of the IVUS catheter in the vessel. The IVUS images were recorded onto a videotape (S-VHS). Also, the images of the important coronary lesions were recorded on Polaroid photographic paper by a printer machine. We evaluated the structure and the lumen size at 65 sites in the coronary arteries of patients with KD (the 5 sites of coronary artery aneurysms, 22 sites of regressed aneurysms, and 38 sites of angiographically normal coronary arteries by IVUS). The findings in patients with KD were then compared with those of the 25 sites in a normal coronary artery of patients with congenital heart disease.

#### Analysis of the Wall Morphology

The coronary wall morphology of the control subjects and of the patients with KD was evaluated by measuring the maximal thickness of several characteristic features of the vessel wall or the echogenicity of the wall structures. The thickness of the intima was measured with an electric cursor. The distance from the lumen–vessel wall interface to the intima-media interface was measured as the width of the intima at the site with three distinct vessel layers of the coronary artery (Fig 1). The severity of the coronary intimal thickening was classified according to the width of the intima: grade 0 (normal), no measurable intimal layer by ultrasound with no evidence of three layers; grade 1 (mild thickening), an intimal layer <0.3 mm thick with three layers; grade 2 (moderate thickening), an intimal layer ≥0.3 mm and <0.6 mm thick; and grade 3 (severe thickening), an intimal layer ≥0.6 mm thick.

#### Measurement of Lumen Size

The smallest axis of the 43 sites in the coronary artery was identified by visual inspection, and the diameter was measured by placing an electronic cursor at the acoustic interface between the lumen and the intimal leading edge at two opposite sides of the...
coronary artery on the IVUS image. Angiographic measurement of the luminal diameters, at the same 43 sites as the IVUS measurements, was made with the cineanalysis system computer (model CAA-100, Nishimoto Sangyo Corp, Osaka, Japan). The right anterior oblique 30° projection or the posteroanterior projection for the left coronary artery and the left anterior oblique 60° projection for the right coronary artery were used for analysis. The measurements by IVUS were done by one of two investigators without knowledge of the angiographic data. Angiographic analysis was performed by another investigator without knowledge of the IVUS data. Each portion was measured three times; the mean values were used for the statistical analysis.

**Statistics**

Two groups were compared by the Wilcoxon test among the groups for the grade of intimal thickening. Quantitative angiographic and ultrasound diameter measurements were compared by simple linear regression analysis. For all analyses, a value of \( P < .05 \) was considered statistically significant.
Results

Clinical Observations

Six patients with coronary aneurysms after KD continued to take aspirin (5 mg/kg per day), whereas the 4 patients with regressed coronary aneurysms and the 2 patients with no coronary abnormal lesion after KD were not administered any drug. No patients with KD had any palpitation, arrhythmias, or myocardial infarction during the follow-up periods. All 12 patients after KD received 201Tl myocardial scintigraphy and an exercise stress test within a week after the follow-up coronary angiography was done, which did not demonstrate any ischemic changes.

Feasibility and Safety of IVUS

Coronary IVUS was effectively performed in all 20 patients. No untoward effects, such as coronary spasm, angina pectoris, or myocardial infarction, were noted in any of the subjects.

Analysis of Wall Morphology

Control. The 25 sites in the coronary arteries of the children with congenital heart disease and a normal coronary artery with no history of KD demonstrated a symmetrical lumen and a smooth homogeneous wall appearance without three layers (Fig 2).

KD with angiographically normal coronary artery. The 10 sites in the angiographically normal coronary artery of the children with a history of KD and no coronary abnormal lesions in the acute stage also demonstrated no thickening of the intima and no measurable three layers (Fig 2).

KD with persistent coronary aneurysms. The 4 sites in the coronary aneurysms of the children with a history of KD demonstrated a dilated symmetrical lumen by a weak echo in the IVUS with no thrombus and no calcification (Fig 3). The images of these sites showed a homogeneous wall appearance with no evidence of three layers and no intimal thickening. It was not possible to measure the width of the intima. The one site in the coronary aneurysms with calcification demonstrated an asymmetrical lumen by a heterogeneous strong echo with acoustic shadows and demonstrated an irregular wall appearance and asymmetrical thickening of intima by a heterogeneous dense echo (Fig 4).

KD with regressed coronary aneurysms. The 7 sites in the regressed coronary aneurysms of the children with a history of KD demonstrated an asymmetrical marked thickening of the intima by a homogeneous dense echo and demonstrated a symmetrical lumen with no calcification and no atheroma by a weak echo in the IVUS (Fig 5, panel 5). The ultrasound image showed the three layers of the intima, media, and adventitia with no irregularity in the lumen. The 15 sites of regressed coronary aneurysms demonstrated a symmetrical marked thickening of the intima by a dense echo and demonstrated a smooth symmetrical lumen with no calcification and no atheroma by a weak echo. The endothelium or the inner intimal leading edge of the coronary artery was smooth in the regressed coronary
aneurysms in the patients after KD. The 9 sites of angiographically normal coronary arteries near the aneurysms in children with a history of KD also demonstrated a mild thickening of the intima with three layers (Fig 5, panel 4). The other 19 sites of the angiographically normal coronary arteries far from the coronary aneurysms or regressed aneurysms in children with a history of KD demonstrated no thickening of the intima and no measurable three layers (Fig 5, panel 3).

Severity of Intimal Thickness

The sites in each group were classified as one of four grades as shown in Table 2. The width of the intima at the 4 sites of coronary aneurysms that was unmeasurable with no evidence of three layers was graded as 0. One site of coronary aneurysm demonstrated a calcification and an intimal thickening and was graded 3. The intima at the 22 sites of the regressed coronary aneurysms (consisting of 2 sites at grade 1, 11 sites at grade 2, and 9 sites at grade 3) had significantly greater thickening compared with the intima at the 28 sites of the portion of the angiographically normal coronary arteries in KD with coronary abnormal lesions (consisting of 19 sites at grade 0, 3 sites at grade 1, and 6 sites at grade 2) (P<.001). The width of the asymmetrical intimal thickening at the 7 sites (all 7 sites at grade 3) of the regressed coronary aneurysms was significantly greater than the symmetrical intimal thickening at 15 sites (consisting of 2 sites at grade 1, 11 sites at grade 2, and 2 sites at grade 3) (P<.001). The 10 sites in KD with no coronary abnormal lesion and the 25 sites in the control group were all at grade 0.

Coronary Lumen Measurements

We measured the vascular dimensions at a total of 43 sites in the coronary artery, comprising 5 sites with congenital heart disease, 3 sites with coronary aneurysms, 15 sites with a regressed aneurysm, and 20 sites of an angiographically normal coronary artery in KD. The diameters measured by coronary angiography were quite similar to the ultrasound diameters (r=.989) (Fig 6, left).

In the regressed aneurysms in patients after KD, the coronary lumen diameters were almost the same as those at the sites of an angiographically normal coronary artery near a regressed aneurysm in the same patients (r=.995) (Fig 6, right).

Discussion

The long-term clinical issues in KD concern the coronary artery lesions and involve aneurysmal formation, thrombotic occlusion, progression to ischemic heart disease, and premature atherosclerosis. However, the long-term pathology of the coronary artery remains uncertain at the present time. Recently, IVUS, a new technology to assess the wall morphology of the vessels, has been performed in vivo or in vitro to evaluate coronary artery lesions in adults.4-12 However, no data are available on the coronary artery in children or in KD. In this study, IVUS was performed in children after KD to seek new insights in this regard.
Several reports regarding IVUS findings from a normal coronary artery in adults have appeared recently. However, no information is available on children. In the normal coronary artery in adults, many investigators have reported that IVUS revealed a three-layered appearance with a bright inner ring, a middle echo-lucent zone, and an outer bright ring. Here, we studied the coronary arteries of children with congenital heart disease and normal coronary arteries as a control group. Unlike in adults, the normal coronary artery in childhood demonstrated no three-layer appearance and a less bright inner ring. There was no apparent middle echo-lucent zone (Fig 2). This suggested that the three-layer appearance in IVUS may develop with aging to adulthood. The intimal layer was classified as abnormal if the coronary artery demonstrated a three-layered appearance in our study.

IVUS at a regressed coronary aneurysm or at a portion of an angiographically normal coronary artery in KD with an abnormal coronary lesion is shown in Fig 5. The portion of the regressed coronary aneurysm demonstrated marked thickening of the intima, but the lumen size was similar to that at sites near a regressed aneurysm that was an angiographically normal coronary artery (Fig 6, right). We have reported that more than half of coronary aneurysms had regressed within a few years from the onset of disease and demonstrated an angiographically normal coronary artery at follow-up.

However, histological examinations demonstrated a marked intimal thickening that may be caused by the proliferation of smooth muscle cells of the media, which in turn makes the artery appear to be of normal size. In this study, we also recognized a marked thickening of the intima in vivo. The width of asymmetrical intimal thickening at the 7 sites of a regressed coronary aneurysm was significantly greater than the symmetrical intimal thickening at the 15 sites of regressed coronary aneurysm. The site of the asymmetrical intimal thickening...
Table 2. Severity of Intimal Thickness in KD

<table>
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<tr>
<th>Coronary Lesions for IVUS</th>
<th>Total</th>
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<th>1</th>
<th>2</th>
<th>3</th>
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<td>25</td>
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<td>0</td>
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<td>KD with CA</td>
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<td>Persistent CA</td>
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<td>4</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
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<td>2</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Symmetrical</td>
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<td></td>
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<td>0</td>
<td>0</td>
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<td>7</td>
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<tr>
<td>Angiographically normal</td>
<td>28</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>portion in patients with CA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KD without coronary lesion</td>
<td>10</td>
<td>19</td>
<td>3</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

KD indicates Kawasaki disease; CA, coronary aneurysm.
Grade 0 indicates unmeasurable intimal layer; grade 1, maximal intimal layer < 0.3 mm; grade 2, 0.3 ≤ maximal intimal layer < 0.6 mm; and grade 3, maximal intimal layer ≥ 0.6 mm.

*P < .001.

The IVUS at the site of a coronary aneurysm several years after the onset of illness demonstrated intimal thickening with calcification (Fig 4). These findings may be similar to the arteriosclerotic changes in coronary artery disease in adults and may be a long-term coronary arteriosclerotic risk factor. Several reports have suggested that IVUS demonstrated a marked intimal thickening in the coronary artery. The coronary artery with arteriosclerosis in adult patients demonstrates an irregularity of the lumen, intimal thickening, or increased echogenicity in the wall or lumen (soft plaque, atheroma, fibrosis, or calcification with an acoustic shadow) in the images. These arteriosclerotic changes, particularly intimal thickening and calcification, were similar to those in the regressed coronary artery after KD. However, the coronary artery after KD demonstrated no increased echogenic plaque suggesting an atheroma in the endothelium or in the intima. In this study, we had no patient with fresh or old thrombus in the coronary artery, so we could not distinguish between fibrosis and lipid-rich atheroma and a fresh or old thrombus by IVUS.

Intimal thickening not only at the site of a regressed coronary aneurysm but also at the site of an angiographically normal coronary artery near an aneurysm or near a regressed aneurysm may suggest that a proliferation of smooth muscle cells, probably due to the healing process after the vasculitis at the acute stage of KD, extends to the proximity of the coronary artery aneurysm. Conversely, however, sites in an angiographically normal coronary artery far from a coronary aneurysm or regressed aneurysm demonstrated normal wall structure with no intimal thickening and no measurable three layers. Patients with a normal coronary artery at the acute stage after KD also demonstrated the same normal findings. The intimal thickening at the site of an angiographically normal coronary artery was

Fig 6. Left, Scatterplot comparing the minimal ultrasound diameter with the angiographic diameter for the sites of a coronary artery after KD. The regression equation was close to the line of identity. Right, Scatterplot comparing the ultrasound diameters at the sites of a regressed coronary aneurysm with their proximal sites. The regression equation was close to the line of identity. IVUS indicates intravascular ultrasound imaging.
significantly less than that at the site of a regressed coronary artery lesion. The abnormal changes at the site of an angiographically normal coronary artery in patients with coronary artery disease were mild. We speculate that if patients have no coronary artery lesion and demonstrate normal coronary angiography, then the wall structure of the coronary artery may be normal or only slightly damaged.

In this study, IVUS was not performed at a site in a stenotic coronary artery after KD, because it was technically difficult to pass the imaging catheter through such a narrow vessel. However, it is important for interventional treatment to evaluate the wall structure of such a stenotic lesion in vivo. For this purpose, we need a smaller imaging catheter in the future.

We have reported that an abnormal coronary artery or regressed coronary artery lesion after KD demonstrated poor distensibility by infusion of isosorbide dinitrate in angiography and had become stiff. IVUS has the ability not only to observe the structure of the coronary artery vessels but also to measure an intraluminal diameter directly in real time and to know the distensibility of the coronary artery. Thus, IVUS may be useful to evaluate not only the morphological changes of a coronary artery but also functional changes.

In conclusion, IVUS is very useful to evaluate the coronary artery wall morphology and function and may contribute to the assessment of long-term coronary artery sequelae and any development of atherosclerotic changes in KD.

Acknowledgments

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