Sequential Follow-Up Results of Catheter Intervention for Coronary Artery Lesions After Kawasaki Disease: Quantitative Coronary Artery Angiography and Intravascular Ultrasound Imaging Study

Masahiro Ishii, MD*; Takafumi Ueno, MD*; Hisao Ikeda, MD; Motofumi Iemura, MD; Tetsu Sugimura, MD; Jun Furui, MD; Yoko Sugahara, MD; Hiromi Muta, MD; Teiji Akagi, MD; Yuichi Nomura, MD; Tomoki Homma, MD; Hiroyoshi Yokoi, MD; Masakiyo Nobuyoshi, MD; Toyojiro Matsuishi, MD; Hirohisa Kato, MD

Background—The purpose of this study was to assess the sequential follow-up results of catheter intervention in Kawasaki disease by use of quantitative coronary angiography (QCA) and intravascular ultrasound imaging.

Methods and Results—Catheter intervention was performed on 23 stenotic lesions in 22 patients (aged 2 to 24 years). Percutaneous balloon angioplasty (PBA) was performed in 4 patients, stent implantation in 7, percutaneous transluminal coronary rotational ablation (PTCRA) in 10, and a combination of PTCRA with stent implantation in 2. A total of 21 lesions (91%) were successfully dilated by catheter intervention without major or minor complications. One patient immediately underwent coronary artery bypass grafting (CABG) surgery because stent implantation failed to resolve his lesion. At 4 to 6 months after catheter intervention, 2 restenotic lesions (9%) were detected by QCA in 2 patients who had undergone PBA, and these patients subsequently underwent CABG surgery. In 6 months to 3 years after catheter intervention, no patients showed evidence of ischemic findings. At 3 to 4 years after catheter intervention, QCA and intravascular ultrasound studies were performed on 15 lesions in 14 patients. Two restenotic lesions (13%) were detected by QCA in 2 patients. One of the 2 had stent implantation and underwent CABG surgery, and the other had undergone PTCRA and underwent re-PTCRA. Thirteen patients demonstrated no ischemic findings at 3 to 8 years after catheter intervention.

Conclusion—Catheter intervention for Kawasaki disease can be accomplished and can be effective in the short term, but the long-term efficacy should be verified by further study. (Circulation. 2002;105:3004-3010.)

Key Words: angioplasty ▪ balloon ▪ pediatrics

Approximately 4% of coronary aneurysms subsequently develop stenotic lesions. Coronary stenosis is a significant cause of sudden death due to myocardial infarction in patients with Kawasaki disease (KD). Catheter intervention for coronary artery lesions is widely performed in adult patients with coronary artery diseases and has provided satisfactory therapeutic results. The coronary artery stenotic lesions in KD commonly involve severe calcification, in contrast with adult coronary artery lesions, which consist primarily of atherosclerosis. Thus, the catheter intervention indicated for adult patients cannot be employed in KD patients. Furthermore, indications of catheter intervention for KD patients have not been established, and the long-term prognosis in KD patients after catheter intervention remains unclear.

Recent advancements in intravascular ultrasound (IVUS) imaging have allowed pathological evaluation of the vascular wall structure of coronary stenosis. Whenever possible, we used IVUS imaging for this evaluation before catheter intervention and then used these results to select a suitable device for catheter intervention. Furthermore, we used IVUS imaging to confirm therapeutic effects and to observe the vascular wall structure during the follow-up period. Accordingly, we assessed the sequential follow-up results in KD patients treated with catheter intervention by use of quantitative coronary angiography (QCA) and IVUS imaging.

Methods

Study Patients
Twenty-two patients, 18 males and 4 females, who developed coronary stenotic lesions caused by KD, were treated with catheter intervention (23 total treatment sites). At the time of the catheter
intervention, the subjects ranged in age from 2 to 24 years (median, 15 years), had been monitored for 2 to 22 years (median, 12 years) after the onset of KD, and had no history of myocardial infarction. The follow-up period after catheter intervention ranged from 7 months to 8 years (median, 4 years). Clinical characteristics of the patients are summarized in the Table.

The Kurume University Ethics Committee gave full ethical approval. Informed consent for the participation of the 2-year-old and the 6-year-old was obtained from their parents before the start of catheter intervention. In the case of all patients aged 9 years or older, informed consent was obtained from both the patient and his or her parents. The catheter interventional treatments were performed at Kurume University Hospital and Kokura Memorial Hospital.

Methods of Catheter Intervention
Percutaneous balloon angioplasty (PBA) was performed in 4 patients by use of a high-pressure balloon (Ranger, Boston Scientific Corp). Stent implantation was performed in 7 patients by use of several types of stent (Table). Percutaneous transluminal coronary rotational ablation (PTCRA) was performed in 10 patients by use of a rotational ablation device (Rota Link PLUS, Boston Scientific Corp), and a combination of PTCRA with stent implantation was performed in 2 patients. One patient (patient 10) was treated twice (PTCRA and stent implantation). For each procedure, interventional success was defined as a stenotic lesion having been reduced to <50% stenosis, as determined by QCA. All procedures were performed with local anesthesia. Any patient with multiple-vessel lesions, ostial lesion, or long segmental lesion was excluded. All catheter interventions were performed without major complications, including blood loss requiring transfusion, malignant arrhythmias, or arterial complications.

QCA Study
The QCA of the left and right coronary arteries was performed by manual injection of iohexol through a 4F Judkins-Ishii pediatric coronary angiography catheter (Filmecc Inc). The minimal lumen diameter (MLD) was measured before and after the catheter intervention and on follow-up studies with the use of the image analyzing system (CARDIO 500, Kontron Elektronic Corp), according to our previous studies.12,14

IVUS Study
The IVUS examination was performed before and after catheter intervention and at follow-up period, as previously reported.11,12 The IVUS examination was performed by use of 30-MHz catheters (3.5F, Boston Scientific Corp). We then measured the thickness of the intima-media complex and calculated the calcification index by use of the following formula: Calcification index (%)=calcification area/area of intima-media complex)x100.

Follow-Up Study Protocol
The acute phase was defined as the period immediately after catheter intervention. The short-term follow-up period was defined as the first 6 months after catheter intervention. Noninvasive follow-up examinations, which included a physical examination, electrocardiography (ECG), and echocardiography, were performed every month. The QCA and IVUS studies were performed at 4 to 6 months after catheter intervention. When coronary stenosis of ≥50% was observed by QCA, it was defined as restenosis. The medium-term follow-up period was defined as the period from 6 months to 3 years after catheter intervention. Noninvasive examinations were carried out every 3 months. Pharmacological stress 99mTc-tetrofosmin scintigraphy dipyridamole infusion (0.56 mg/kg), and treadmill exercise-stress ECG (according to the Bruce protocol) were performed every year. The long-term follow-up period was defined as the period of 3 years after catheter intervention and beyond. The QCA and IVUS studies were performed at 3 to 4 years after catheter intervention. Noninvasive examinations were performed every 4 months, and the stress tests were performed every 2 years during the long-term follow-up period.

Statistical Analysis
Quantitative variables were expressed as the mean±SD. Logistic univariate and multivariate regression analyses were used to determine the effects of five variables, including age at onset of KD, age at intervention, term from onset of KD, calcification index, and MLD, on the outcome of catheter intervention. Two independent observers, each of whom individually selected the frames to measure MLD and calcification index, and had no knowledge of the results obtained by the other observer, analyzed 10 randomly selected patients at different times. Differences were considered significant at 𝑃<0.05.

Results
Acute Phase
Twenty-one of 23 stenotic lesions (91%) in 22 patients were successfully dilated by catheter intervention without major or minor complications (Figure 1). The MLD ranged from 0 to 1.7 mm (1.2±0.4 mm) before intervention (Table). The calcification index ranged from 14% to 100% (59±27%) before intervention. The PBA resolved 4 stenotic lesions in all 4 patients (100%) (Figure 2A, 2B). The stent implantation resolved 6 stenotic lesions with mild to moderate degrees of calcification detected by IVUS imaging (calcification index: <75%) in 6 of the 7 patients (86%) (Figure 3A, 3B). The stent implantation failed to resolve the stenotic lesion in one patient (patient 15) in whom severe calcification was observed by IVUS imaging (calcification index: 100%, Figure 4A, 4B). This patient immediately underwent coronary artery bypass grafting (CABG) surgery. The PTCRA resolved 9 stenotic lesions in 9 of the 10 patients (90%) (Figure 5A, 5B). The PTCRA resolved stenotic lesions with severe calcification (calcification index: ≥75%). The PTCRA failed to resolve the stenotic lesion in one patient (patient 6), whose body size was too small to allow the use of an appropriately sized burr. The patient still had 50% stenosis after PTCRA, but his ischemic findings, defined by pharmacological stress scintigraphy, improved. The combination of PTCRA with stent implantation was performed in 2 stenotic lesions in 2 patients with severe calcification (calcification index: ≥75%). First, PTCRA was performed before the stent implantation to reduce the calcification index; immediately thereafter, the stent implantation successfully enlarged the stenotic lesions (success rate: 100%) (Figure 6A, 6B, and 6C). The univariate and multivariate logistic regression analysis identified no significant relationship between 5 variables and the outcome of catheter intervention (𝑃=0.16 to 0.99).

Short-Term Examination
The QCA and IVUS studies were performed in 22 lesions on 21 patients at 4 to 6 months after catheter intervention in the entire cohort, except for the 1 patient (patient 15) who underwent CABG surgery immediately after stent implantation. Two restenotic lesions (9%) were detected by QCA in 2 patients undergoing PBA (Figure 1). In 1 patient (patient 20) who underwent PBA, ischemic symptoms were manifested during the short-term follow-up period, and complete occlusion was observed by QCA at 4 months after the PBA (Figure 2C). This patient immediately underwent CABG surgery. In another patient (patient 19) who underwent PBA, a complete occlusion was observed by QCA at 6 months after PBA, and
CABG surgery was subsequently performed. In the other 20 lesions of 19 patients, no significant development of restenosis was observed by QCA at 4 to 6 months after catheter intervention (Figure 1). Neither neointimal hyperplasia nor a progression of calcification was observed by IVUS imaging. A neo-aneurysm developed in 4 of the 22 lesions (18%) during the short-term follow-up period. The 4 neo-aneurysms consisted of 2 lesions in the 2 patients undergoing PBA, 1 lesion from the 1 patient undergoing stent implantation, and 1 lesion from the 1 patient undergoing PTCRA. In 3 of the 4 cases with a neo-aneurysm, the expanded balloon pressure was 12 atm or higher (Table).

Medium-Term Follow-Up Examination
The medium-term follow-up examination was performed in 19 patients. The entire cohort, except 1 patient, underwent CABG surgery at acute phase, and 2 underwent CABG surgery during the short-term follow-up period. The follow-up periods ranged from 7 months to 3 years. No patient had any ischemic symptoms, such as chest pain, or any evidence of ischemic findings detected by stress test (Figure 1).

Long-Term Follow-Up Examination
Fourteen patients were followed up beyond 3 years after catheter intervention, ranging from 3 to 8 years (median 5 years). The 15 lesions on these 14 patients were examined by use of QCA and IVUS imaging at 3 to 4 years after catheter intervention. Two restenotic lesions (13%) were observed by QCA in 2 patients. The CABG was performed in 1 patient (patient 13) previously treated by stent implantation. The re-PTCRA was performed in 1 patient (patient 4) previously treated with PTCRA. One patient (patient 10) was treated twice (PTCRA and stent implantation) because another stenotic lesion had developed during the 3 years after PTCRA.

In patient 14, a 19-year-old-girl, no significant restenosis was observed by QCA at 3 years after stent implantation (Figure 3C); however, a mild degree of neointimal hyperplasia was confirmed by IVUS imaging in stent (Figure 3D). In the other 11 patients, no significant restenotic lesions were observed by QCA (Figure 5C), and no neointimal hyperplasia or development of calcification was detected by IVUS imaging (Figure 5D) at 3 to 4 years after catheter intervention. We continued to follow up these 13 patients for 3 to 8 years (median, 5 years) after catheter intervention, with the exception of 1 patient who underwent CABG surgery, and none of the patients showed any ischemic symptoms or findings by stress tests.

Reproducibility of Measurements
An excellent correlation was found between the MLD of QCA measurements made by the 2 independent observers (r=0.95, P<0.001, mean difference 0.21±0.03 mm). Significant correlation and agreement were found between the IVUS calcification index measurements of the 2 observers (r=0.94, P<0.001, mean difference 2.5±1.8%).

Discussion
Comparison With Previous Studies
Catheter intervention for stenotic lesions in KD is currently performed in only a limited number of cases. Previous studies have demonstrated that PBA is effective for patients within 6 years of the onset of KD, but at >6 years after onset, it is less effective.5,8,15 In the present study, PBA successfully resolved stenotic lesions in 3 patients for whom the time since onset of KD had been <4 years. There have been a few reports in which stent implantation, a technique of coronary intervention commonly performed in adult patients, was applied to KD patients.6,9,16,17 In the present study, we performed stent
Figure 1. Sequential evaluation of catheter intervention outcomes. n indicates the number of lesions. Patient 10 was treated twice (PTCRA and stent implantation) because another stenotic lesion had developed during the 3 years after PTCRA. Although there might not have been a worsening of stenosis after intervention in patient 6, the primary intervention was unsuccessful.
implantation in 7 patients, with the results demonstrating that the incidence of neo-aneurysm after stent implantation was less than that after PBA alone, despite the use of a high balloon pressure. In the present study, PTCRA was performed in 10 patients and was demonstrated to be especially effective for stenotic lesions with severe calcification, as shown in our previous report.7

Outcome of Catheter Intervention in KD Patients
The safety and long-term efficacy of catheter intervention for KD remains unclear. Although mortality was nil in the present study, 1 patient acutely and 2 in the short term required “immediate” CABG surgery. Additionally, 4 patients developed neo-aneurysm after catheter intervention. Further study may be necessary to clarify the safety of catheter intervention in large numbers of KD patients. The ratio of restenosis evaluated by QCA in the present study was 9% in the short-term and 13% in the long-term follow-up. These ratios of restenosis are much lower than that of catheter intervention for arteriosclerotic lesions in adults.18 In addition, hyperplasias of abnormal endothelium were not observed with IVUS imaging during the follow-up period in almost all cases (Figure 5D). The normal neo-endothelium may derive from media that preserves normal function and structure, as previous pathological studies have indicated.3,19

Selection of an Appropriate Device for Catheter Intervention in KD
In the present study, catheter interventions were performed with the use of PBA, stent implantation, or PTCRA. There are currently no established criteria for selecting these devices. Our proposed criteria for device selection are summarized here on the basis of the results from present and previous studies.5–9,15–17 It is well known that PBA alone is less effective for long-term lesions with severe calcification.5–9 Half of all coronary artery stenotic lesions, however, occur within 2 years of KD onset.1 In these cases, the stenotic

Figure 2. A 9-year-old boy (patient 20) with localized, severe stenosis (99%) at the left anterior descending coronary artery (LAD) (A), in whom PBA was subsequently performed. The stenotic lesion was successfully dilated by a balloon with pressure as low as 6 atm (B). Coronary angiography demonstrated the complete occlusion of LAD (C) at 4 months after PBA.

Figure 3. Left coronary angiogram of a 16-year-old girl (patient 14) with 75% stenosis on proximal LAD (arrows) (A). The stenosis improved from 75% to 25% after stent implantation (B). No significant development of restenosis was observed with QCA at 3 years after the stent implantation (C); a mild degree of neointimal hyperplasia was confirmed with IVUS imaging (D).

Figure 4. Right coronary angiogram of a 16-year-old boy (patient 15) (A). In this case, the coronary artery stenosis did not improve after stent implantation. IVUS imaging at the site of the coronary artery showed a circumferential, thick, ring-shaped severe calcification (calcification index: 100%) (B).
lesions are caused primarily by intimal hypertrophy without calcification. In such cases, PBA is considered to be the first choice. We performed either the stent implantation or PTCRA in long-term cases. We decided on a therapeutic procedure after pathological observation of the stenosis with IVUS imaging. The stent implantation was performed in cases with comparatively mild calcification, ≤50% on the calcification index, whereas PTCRA was selected in cases with more severe calcification. When insufficient expansion occurred with PTCRA alone, a stent implantation was also performed, provided that the calcification index was <50% by IVUS imaging. Some institutions utilize PTCRA for all KD patients, as it is effective for stenotic lesions with severe calcification. However, PTCRA produces a higher risk of fatal complications, such as coronary artery perforation and cardiac tamponade, as compared with either PBA or stent implantation. Our institution, therefore, uses IVUS observation to select a suitable device that will present a lower risk to the patient.

In one patient (patient 14), the development of significant stenotic lesions was not detected by QCA, but a mild degree of intimal hyperplasia inside the stent was observed with IVUS imaging at 3 years after stent implantation (Figure 3C and 3D). This patient, like the others, had no risk factors for arteriosclerosis. The clinical significance of this finding is unclear. The long-term follow-up IVUS study is essential to evaluate the vascular wall morphology after intervention to determine the long-term effects of catheter intervention.

**Indication of Catheter Intervention for Coronary Artery Stenotic Lesions in KD**

American College of Cardiology/American Heart Association guidelines indicate that catheter intervention may be performed in adult patients with ischemia. In the present study, catheter intervention was performed in patients with stenotic lesions of ≥75%, even if no evidence of ischemia was detected by any stress tests. The guidelines for catheter intervention in KD, published by the research committee of the Japanese Ministry of Health, Labor, and Welfare, indicate that patients with severe stenotic lesions in the left anterior descending coronary artery can be considered candidates for catheter intervention because this condition runs a risk of sudden death due to myocardial infarction.

**Study Limitations**

The present study was not a multicenter study like those commonly performed to investigate catheter intervention in adult patients with coronary artery disease. In the present study, the catheter interventions were performed at 2 institutions, both leading hospitals in Japan, by 4 catheter-intervention specialists (T.U., H.T., H.Y., and M.N.). The present study, therefore, may not fully represent variations in technical expertise among institutions in the manner of multicenter studies. Accordingly, a prospective, multicenter study may be necessary to clarify the long-term prognosis of catheter intervention in KD. In the long term, 13 patients had no ischemic symptoms or findings by several stress tests; however, these findings may not fully represent long-term success, inasmuch as stress tests on patients with KD with severe stenosis often show no ischemic symptoms or findings.

**Conclusions**

Catheter intervention for coronary artery stenotic lesions in KD demonstrated significant therapeutic effects in the short term. The long-term efficacy of catheter intervention for KD...
is unclear. To verify this finding, more long-term follow-up studies are needed.

Acknowledgments
This study was supported in part by Grants-in-Aid 12670789 and 14570786 from the Ministry of Education, Science, and Culture and The Mother and Child Health Foundation, Japan.

References
Sequential Follow-Up Results of Catheter Intervention for Coronary Artery Lesions After Kawasaki Disease: Quantitative Coronary Artery Angiography and Intravascular Ultrasound Imaging Study

Masahiro Ishii, Takafumi Ueno, Hisao Ikeda, Motofumi Iemura, Tetsu Sugimura, Jun Furui, Yoko Sugahara, Hiromi Muta, Teiji Akagi, Yuichi Nomura, Tomoki Homma, Hiroyoshi Yokoi, Masakiyo Nobuyoshi, Toyojiro Matsuishi and Hirohisa Kato

_Circulation_. 2002;105:3004-3010; originally published online June 3, 2002;
doi: 10.1161/01.CIR.000019733.56553.D8

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/105/25/3004

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/