Coronary Artery Distensibility in Kawasaki Disease

—Evaluation by Intracoronary Infusion of Isosorbide Dinitrate in Long-Term Follow-Up—

TETSU SUGIMURA

*Department of Pediatrics and Child Health, Kurume University School of Medicine,
Kurume, 830 Japan*

Received for publication October 15, 1991

Summary: The coronary artery lesions in Kawasaki disease (KD) are thought to be a possible risk factor for atherosclerosis in the long term from the pathological point of view. Here we report results of a comparative control study to investigate the distensibility of the coronary artery in KD. A total of 146 patients were divided into 5 groups as follows. (I) Normal group (N); consisting of 44 patients with a known history of KD but with no coronary artery lesion. Among this group of patients those who each showed a regression in their coronary artery aneurysms were divided into 2 subgroups according to the time since onset of KD. (II) A group in the early stage after regression (ER); consisting of 18 patients with a known history of KD followed for 1.8 ± 0.6 years. (III) A group in the later stage after regression (LR); consisting of 22 patients with a known history of KD followed for 9.4 ± 2.8 years. (IV) an abnormal group (A); consisting of 21 patients followed for 7.9 ± 4.0 years with a persistent aneurysm and/or stenosis in a coronary artery at the time of this study. And (V) a control group (C); consisting of 41 patients with a congenital heart disease such as a small ventricular septal defect or mild pulmonary stenosis or patent ductus arteriosus and no history of KD. In each case, the coronary artery diameter was measured by angiography before and after intracoronary infusion of isosorbide dinitrate (ISDN). Then, the percent change in the coronary artery diameter was calculated as follows; $\langle (\text{After ISDN} - \text{Before ISDN}) / \text{Before ISDN} \times 100 \rangle$. The percent changes were $16.168 \pm 12.494\%$ (N), $11.622 \pm 6.975\%$ (ER), $9.891 \pm 9.190\%$ (LR), $6.338 \pm 7.723\%$ (A), and $14.561 \pm 11.652\%$ (C), respectively. In the A group, there was significantly poorer distensibility compared with C, N, or ER group. And the LR group also demonstrated significantly poorer distensibility compared with the N group ($P < 0.05$). Results of this study suggest that the coronary artery in KD may become stiff not only in the persistent abnormal lesion but also possibly in the regressed aneurysm over the long term. Such stiffness may then constitute a risk factor for atherosclerosis.

Key words: Kawasaki disease — Isosorbide dinitrate — Distensibility — Coronary aneurysm — Regression — Atherosclerosis

Introduction

Kawasaki disease (KD) is an acute febrile vasculitis mainly affecting infants and young children. Since Kawasaki first reported this acute febrile mucocutaneous syndrome with lymphoid involvement (Kawasaki, 1967), it has become recognized as a major pediatric disorder worldwide. Ten to twenty percent of these patients develop a coronary aneurysm, which is the most serious complication, because coronary aneurysms may cause sudden death or ischemic heart disease due to thrombotic or stenotic occlusion of the coronary artery. The incidence of the aneurysm developing into ischemic heart disease is about three percent (Kato et al. 1982; Kato and Ichinose, 1984). We have reported that 60% of patients with a coronary aneurysm demonstrated regression of the aneurysm, by follow-up coronary angiography (Kato et al. 1974, 1975 and 1982). [Current therapy for the acute stage of KD involves intravenous administration of high dosage gamma-globulin (IVGG) plus aspirin, and this reduces considerably the incidence of coronary artery abnormalities (Furusho 1984; Newburger 1986 and 1991). However some cases in KD become complicated with a coronary aneurysm despite administration of IVGG. Now more than 20 years have passed since Kawasaki first described this entity (Kawasaki 1967), so many children with a known history of KD have now become adults.

The pathohistological findings of a regressed aneurysm demonstrates a marked thickening of the intima with proliferation of smooth muscle cells (Sasaguri et al. 1979; Sasaguri and Kato. 1982). Naoe et al. and Fujiwara et al. have reported that a transient dilatation in the coronary artery in acute KD was related with a proliferation of intima, thinness of media, and rupture of the lamina elastica interna (Naoe et al. 1987; Fujiwara et al.

1988). These pathohistological changes are very similar to the findings in arteriosclerosis (Sasaguri et al. 1979; Masuda et al. 1981; Naoe et al. 1983). These pathohistological changes of the coronary artery in KD may therefore become an atherosclerotic risk factor with increasing age. The distensibility of the coronary artery in KD was therefore investigated in 146 patients by intracoronary infusion of isosorbide dinitrate (ISDN).

Patients and Methods

Patients

From July 1988 through May 1991, 146 patients underwent coronary angiography after intracoronary infusion of ISDN at Kurume University Hospital. These patients were divided into five groups as follows to investigate the distensibility of the coronary artery in children with KD. (I) the normal group (N) consisted of 44 patients with KD but with no abnormal coronary findings in coronary angiograms performed up until after the acute stage of the illness. Among this group of patients those who showed a regressed coronary aneurysm were then divided into 2 groups according to the time since onset of KD. (II) the group in the early stage after regression (ER) consisted of 18 patients with KD who had a coronary aneurysm in the first coronary angiogram, which disappeared in a follow-up coronary angiogram performed within 3 (1.8 ± 0.6) years from the onset of KD. (III) the group in the late stage after regression (LR) consisted of 22 patients with KD who had a regressed coronary aneurysm, and had been followed for more than 5 (9.4 ± 2.8) years from the onset. (IV) the abnormal group (A) consisted of 21 patients with KD who had a persistent coronary aneurysm and/or stenosis, and had been followed for 7.9 ± 4.0 years. And (V) the control group (C) consisted of 41

patients with normal coronary artery and a congenital heart disease such as a small ventricular septal defect or mild pulmonary stenosis or patent ductus arteriosus and no history of KD (Table 1).

Coronary angiography

A 6F sheath was inserted percutaneously into the femoral artery, through which a 5F Judkins-Kato pediatric coronary angiographic catheter was advanced up to the ostium of the right or left coronary artery using the Judkins' technique. We measured the systemic arterial pressure through the Judkins-Kato coronary angiographic catheter, and the heart rate by electrocardiographic monitoring. The baseline heart rate and arterial pressure were recorded, and cineangiography of the left and right coronary arteries was performed by injection of Iohexol manually under electrocardiographic monitoring. The cineangiosystem was model KXO-2050 (Toshiba Corporation, Kawasaki, Kanagawa, Japan). After the baseline recordings and cineangiography, we slowly infused over 5 minutes ISDN (0.01 mg/kg, Max. 0.5 mg) diluted in 2~3 ml of warm 0.9% saline into the right or left coronary artery. The second cineangiography was performed in both coronary arteries 2 minutes after the completion

of the ISDN infusion.

Angiographic Analysis

The measurement sites for the luminal diameters were the proximal portion of the left anterior descending artery, the left circumflex artery and the right coronary artery. The right anterior oblique 30° projection or the posterior anterior projection for the left coronary artery and the left anterior oblique 60° projection for the right coronary artery were taken for analysis. The cine frame for measurement was at the end of the diastolic phase. The luminal diameters were measured quantitatively using the cineanalysis system computer (model CAA-100, ELK Corporation, Nagoya, Aichi, Japan or Kontron Bildanalyser, KONTORON Electronic Group, Eching, Munich, Germany) using delineation of the coronary cineangiograms before and after the ISDN infusion. Figure 1 and Figure 2 show the angiograms of the left coronary artery before and after the ISDN infusion. We took measurements three times and used the average for each portion. The external diameter of the coronary catheter proximal to the primary curve was used as a scaling device to determine the absolute diameter. At a coronary aneurysm, measurement sites were proximal and

TABLE 1
Patients

	n	AGE (years)	TERM (years)
Control ^①	41	4~17 (9.0±3.6)	
Kawasaki disease			
Normal	44	1~17 (8.1±4.7)	1.2~10.3 (5.2±4.2)
Early stage after regression	18	1~7 (4.2±1.9)	1.1~3.0 (1.8±0.6)
Late stage after regression	22	8~17 (12.1±2.8)	5.8~14.0 (9.4±2.8)
Abnormal ^②	21	5~17 (11.1±3.6)	2.0~14.0 (7.9±4.0)

n: number of patients. AGE (mean ± standard deviation): age at time of study. TERM (mean ± standard deviation): time from onset of KD to study. ①: patients had a small ventricular septal defect or mild pulmonary artery stenosis or patent ductus arteriosus without KD. ②: KD cases with aneurysm and/or stenosis of coronary artery.

Distensibility of coronary artery infused by Isosorbide dinitrate (ISDN)

Fig. 1. Coronary angiogram (posterior anterior projection) of the left coronary artery before and after ISDN infusion in a case of patent ductus arteriosus after operation without KD history. The coronary artery is dilated by the ISDN infusion.

Distensibility of coronary artery infused by Isosorbide dinitrate (ISDN)

Fig. 2. Angiograms and densitometric analyses demonstrating the dilatation in the left coronary artery by the ISDN infusion in a child with KD history. The left coronary artery diameter increased from 3.32 mm to 3.51 mm after the ISDN infusion.

distal to the aneurysm, and the average of both values was taken to be the effective value.

Calculation

The coronary artery distensibility (the percent change in the coronary artery diameter) was calculated by the following formula: percent change in coronary artery diameter = (coronary artery diameter after ISDN infusion - coronary artery diameter before ISDN infusion) / coronary artery diameter before ISDN infusion $\times$ 100.

Statistics

The percent change in coronary artery diameter is presented as a mean value with standard deviation. Two groups were compared using Student's *t* test,

among the 5 groups. For all analyses, a *p*-value less than 0.05 was considered statistically significant.

Results

The coronary artery distensibility

The coronary artery diameters in each patients were measured before and after intracoronary infusion of ISDN, and the percent changes in the coronary artery diameter were calculated for each patient. The percent changes in the coronary artery diameter in each group are shown in Fig. 3. The distensibility of the coronary artery was $16.168 \pm 12.494\%$ in the N group, $11.622 \pm 6.975\%$ in the ER group, $9.891 \pm 9.190\%$ in the LR group, $6.338 \pm 7.723\%$ in the A group and 14.561 ± 11.652

**Percent Changes in Distensibility of a Coronary Artery
by Intracoronary ISDN Infusion**

Fig. 3. Percent change in the coronary artery diameter by intracoronary ISDN infusion in the control group, the normal group, the group in early stage after regression, the group in late stage after regression, and in the abnormal group. A *p*-value less than 0.05 was considered statistically significant.

% in the C group respectively. In the A group, there was a significantly poorer distensibility compared with that in the C group ($p=0.0049$), the N group ($p=0.0016$), and the ER group ($p=0.0322$). In the LR group, there was also a significantly poorer distensibility compared with that in the N group ($p=0.0407$), while the N group demonstrated no significantly different distensibility compared with the C group.

Complication

The hemodynamic examinations including heart rate and aortic pressure showed no change during this study. Changes of ST segment in the electrocardiogram were observed in some patients during the intracoronary infusion of ISDN. However these changes were transient. No child had any complaints with the intracoronary infusion of ISDN.

Discussion

The long-term prognosis or natural history of KD, particularly in adulthood, is unknown. The state of the coronary arteries in KD, particularly in KD without coronary aneurysms, over the long-term is therefore of interest pathologically. The coronary artery aneurysm in KD generally shows thinning of the media, rupture of the lamina elastica interna or thickening of the adventitia in pathohistological findings (Sasaguri et al. 1979; Masuda et al. 1981; Naoe et al. 1983 and 1985). We have further reported (Kato et al. 1974, 1975 and 1982) that some aneurysms have become angiographically normal. However, at a pathohistological examination the regressed artery has a thick intima, which may be caused by proliferation of smooth muscle cells (Sasaguri et al. 1979; Sasaguri and Kato, 1982). Fujiwara et al. have reported an abnormal fibrous intimal thickening

in the coronary arteries of KD children without any coronary arterial aneurysm (Fujiwara et al. 1988). There is no report so far that these abnormal changes in the intima are related to atheroma or foam-cell in KD. However, the thickening of the intima is similar to that found in arteriosclerosis, and could later be responsible for ischemic heart disease simulating atherosclerosis (Sasaguri et al. 1979; Masuda et al. 1981; Naoe et al. 1983). Many reports have discussed the morphological and pathohistological findings of the coronary arteries in KD, but few have been concerned with the functional behavior of the coronary arteries. Here we report the results of a functional evaluation of the coronary arteries in KD with and without a coronary lesion, using intracoronary infusion of ISDN, using selective coronary angiography.

Changes in the coronary arterial diameter were observed after the ISDN infusion into the coronary artery (Figs. 1, 2). The results clearly show that in the abnormal coronary artery with KD, there was a significantly poorer distensibility compared with the coronary artery without KD, the normal coronary artery with KD, or the coronary artery at an early stage after regression. The coronary artery at a late stage after regression also demonstrated a significantly poorer distensibility compared with a normal coronary artery with KD (Fig. 3). Kurisu et al. reported that the distensibility in the group of children with disappearing aneurysms in KD was significantly lower than that in the control group, by cineangiography using a distensibility index {the index = (maximal diameter - minimal diameter) / minimal diameter} for analysis (Kurisu et al. 1987). On the other hand, Ono et al. reported that the coronary artery diameters in the dilated or aneurysmal lesions in KD revealed no change after an intracoronary infusion of dipyridamole. However the regressed coro-

nary aneurysm in KD showed a distensibility similar to that of a coronary artery without an aneurysm in KD (Ono et al. 1985). In the report by Ono et al., the time since onset of KD of children who had a regressed coronary artery was 0.75 years (mean). These patients correspond to those of the ER group in this study. No significant difference in distensibility was found between the regressed coronary artery of KD with an aneurysm and the coronary artery without aneurysm. In this study, the coronary artery in the late stage after regression demonstrated a significantly poorer distensibility compared with a normal coronary artery of KD. However the coronary artery in the early stage after regression demonstrated no significant difference in distensibility compared with a normal coronary artery of KD. This result may be due to the fact that the wall of the coronary artery of

KD becomes stiffer with increasing age. In other studies, the methods used to evaluate the distensibility varied. We have also investigated the distensibility using an intravascular ultrasound image (Fig. 4). In this study the data suggest that the coronary artery of KD was stiff not only in the persistent abnormal lesions included an aneurysm and/or stenosis but also in the regressed coronary aneurysm. The cause of such stiffness may be the intimal thickening due to proliferation of smooth muscle cells in the coronary artery in KD. Since an intimal thickening in the coronary artery was reported in children with KD without a coronary aneurysm (Fujiwara et al. 1988), then the coronary artery of KD without a coronary aneurysm may also develop stiffness with increasing age. Such developing stiffness may be a risk factor for atherosclerosis in the long term. Ac-

Distensibility of Coronary Artery Infused by Isosorbide Dinitrate (ISDN) in Intravascular Ultrasound Image

Fig. 4. Intravascular ultrasound images of the right coronary artery before and after ISDN infusion in a 13-year-old male with KD history. In this image, the arterial lumen demonstrated a weak echo, and the adventitia a strong echo, so that the diameter of the coronary arterial lumen could be measured from this Figure. In this case the coronary artery diameter was increased from 2.9 mm to 3.6 mm by the intracoronary ISDN infusion.

cordingly we should follow-up carefully these patients paying attention to ischemic heart disease, and should manage them to reduce other risk factors such as hypertension, smoking, and hypercholesteremia.

Conclusions

1) The distensibility of the coronary artery was evaluated by an intracoronary infusion of isosorbide dinitrate in Kawasaki disease.

2) In the coronary artery of KD with a persistent coronary aneurysm and/or stenosis, there was a significantly poorer distensibility compared with the coronary artery without KD, the normal coronary artery with KD, or the coronary artery at an early stage after regression. And the coronary artery at a late stage after regression also demonstrated a significantly poorer distensibility compared with a normal coronary artery of KD.

3) These results suggest that the coronary artery wall in KD may become stiff not only in the persistent abnormal artery but also in a regressed aneurysm, and therefore may become a long-term risk factor for atherosclerosis.

Acknowledgment: The author thanks Professor Fumio Yamashita, chairman of pediatrics, and Professor Hirohisa Kato, director of pediatric cardiology for their advice and comments, and also Dr. Osamu Inoue and Dr. Junichi Takagi for technical cooperation.

References

- FUJIWARA, T., FUJIWARA, H. and NAKANO, H. (1988). Pathological features of coronary arteries in children with Kawasaki disease in which coronary arterial Aneurysm was absent at autopsy. *Circulation* **78**, 345-350.
- FURUSHO, K., KAMIYA, T., NAKANO, H., et al. (1984). High-dose intravenous gamma globulin for Kawasaki disease. *Lancet* **2**, 1055-1058.
- KATO, H., KOIKE, S., YAMAMOTO, M., ITO, U. and YANO, E. (1974). Coronary artery aneurysms in mucocutaneous lymph node syndrom; Angiographic study. (in Jpn). *Jpn. J. Pediatr.* **27**, 789-798.
- KATO, H., KOIKE, S., YAMAMOTO, M., ITO, U. and YANO, E. (1975). Coronary artery aneurysms in infants and young children with acute febrile mucocutaneous lymph node syndrome. *J. Pediatr.* **86**, 892-898.
- KATO, H., ICHINOSE, E., YOSHIOKA, F., et al. (1982). Fate of coronary aneurysms in Kawasaki disease; Serial coronary angiography and long term follow up study. *Am. J. Cardiol.* **49**, 1758-1766.
- KATO, H. and ICHINOSE, E. (1984). Clinical presentations and cardiovascular problems in Kawasaki disease. (in Jpn). *Pediatric Review* **17**, 960-998.
- KAWASAKI, T. (1967). Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children. (in Jpn). *Jpn. J. Allergy* **16**, 178-222.
- KURISU, Y., AZUMI, T., SUGAHARA, T., et al. (1987). Variation in coronary arterial dimension (distensible abnormality) after disappearing aneurysm in Kawasaki disease. *Am. Heart. J.* **114**, 532-538.
- MASUDA, H., NAOE, S. and TANAKA, N. (1981). A pathological study of coronary artery in Kawasaki disease (MCLS). (in Jpn). *J. Jpn. Coll. Angiol.* **21**, 899-912.
- NAOE, S., ATOBE, T., MASUDA, H., et al. (1983). Kawasaki disease-particularly on arterial changes. (in Jpn). *Pathol. Clin. Med.* **1**, 1156-1166.
- NAOE, S., ATOBE, T., ANDO, M., et al. (1985). Clinicopathological examination of Kawasaki disease-morphogenesis of coronary artery aneurysm. (in Jpn). *Prog. Med.* **5**, 21-27.
- NAOE, S., TAKAHASHI, K., MASUDA, H., et al. (1987). Coronary findings post Kawasaki disease in children who died of other causes. In *Kawasaki disease*, pp. 341-346. New York: Alan R. Liss Inc.
- NEWBURGER, J. W., TAKAHASHI, M., BURNS, J. C., et al. (1986). The treatment of Kawasaki syndrome with intravenous gamma globulin. *N. Engl. J. Med.* **315**, 341-347.
- NEWBURGER, J. W., TAKAHASHI, M., BEISER, A. S., et al. (1991). A single intravenous infusion of gamma globulin as compared with four infu-

- sions in the treatment of acute Kawasaki syndrome. *N. Engl. J. Med.* **324**, 1633-1639.
- ONO, S., SONE, K., SUZUKI, T., et al. (1985). Clinical evaluation of coronary dilated lesions in Kawasaki disease by intracoronary dipyridamole. (in Jpn). *J. Jpn. Pediatr. Society* **89**, 649-654.
- SASAGURI, Y., KATO, H., KOIKE, S., et al. (1979). Pathological examination of the multiple coronary aneurysms in Kawasaki disease. (in Jpn). *Jpn. J. Pediatr.* **32**, 1521-1529.
- SASAGURI, Y. and KATO, H. (1982). Regression of aneurysms in Kawasaki disease; a pathological study. *J. Pediatr.* **100**, 225-231.