—**Original**—

Optimal Time of Surgical Treatment for Kawasaki Coronary Artery Disease

Hitoshi Yamauchi[1], Masami Ochi[1], Masahiro Fujii[1], Kazuhiro Hinokiyama[1], Hiroya Ohmori[1], Takashi Sasaki[1], Ei Ikegami[1], Yoko Uchikoba[2], Shunichi Ogawa[2] and Kazuo Shimizu[1]

[1]Division of Cardiovascular Surgery Department of Surgery, Nippon Medical School
[2]Department of Pediatrics, Nippon Medical School

Abstract

Background: The major complication of Kawasaki coronary disease is myocardial infarction caused by thrombus formation inside the aneurysm or by organic obstructive lesion following the regression of aneurysm, while the indications for surgical therapy remain controversial. We have adopted coronary artery bypass grafting (CABG) even in young children for giant coronary aneurysms (more than 8 mm diameter) with or without a stenotic region when myocardial ischemia is detected. We hypothesized that a shorter time-period from diagnosis of acute Kawasaki disease (KD) to CABG would lead to better postoperative results. To elucidate the validity of our strategy, we evaluated preoperative patient characteristics and long-term outcome.

Methods: Twenty-one patients (mean age: 12.0 years old) with Kawasaki coronary disease had undergone CABG during the last 12 years. The mean age at the time of acute KD was 2.7 years and the mean time range from diagnosis of acute KD to CABG was 8.1 years. The incidence of preoperative reduced ventricular function was 10 per 21 patients (47.6%). A multivariate logistic regression analysis using patient characteristics showed that the time range from acute KD to CABG was the only predictor for ventricular functional deterioration ($p = 0.03$, odds ratio 1.55. 95%CI: 1.033～2.325). Based on these results, we divided the patients into two groups of short time range (mean: 3.7 years; group S) and long time range (mean: 13.9 years; group L).

Results: Preoperative left ventricular functional deterioration was recognized more frequently in group L (9/9, 100%) than in group S (1/12, 8.3%) ($p < 0.01$). Myocardial infarction was documented significantly higher in the group L (6/9, 66.7%) than group S (1/12, 8.3%) ($p = 0.04$). There was no surgical mortality in either group. The arterial grafts demonstrated good potential for growth and graft patency was 96.9%. Moreover, seven of the giant aneurysms proximal to the graft anastomosis showed complete thrombotic occlusion after CABG without development of myocardial infarction. The cardiac events free rate of group L and group S was 66.7% and 100%, respectively, during the postoperative follow up periods of 5.5 ± 1.1 years (group L) and 4.7 ± 1.1 years (group S).

Conclusions: We successfully applied CABG for Kawasaki coronary disease. Based on our experience, a short interval after acute KD appears to be ideal for surgical treatment of Kawasaki coronary disease.

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Key words: coronary artery bypass grafting, coronary artery aneurysm, Kawasaki disease

Correspondence to Hitoshi Yamauchi, MD, Division of Cardiovascular Surgery Department of Surgery, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8603, Japan
E-mail: hito-y@nms.ac.jp
Journal Website (http://www.nms.ac.jp/jnms/)

Introduction

Mucocutaneous lymph node syndrome was termed Kawasaki disease (KD) after the physician who first described this disease in 1967[1]. KD is diffuse and systematic vasculitis of unknown etiology that occurs in infants and young children[2]. It is well-known that 10～20% of patients with KD have coronary artery complications in the acute stage, while approximately 4% of all patients may progress to ischemic heart disease[3–5]. Recent studies have shown the efficacy of coronary artery bypass grafting (CABG)[6] and catheter intervention[7,8] for obstructive lesions of the coronary arteries in KD; however, optimal time of surgical treatment still remains controversial. One of the major complications of KD is thrombus formation in the coronary aneurysms. 30% of giant coronary aneurysms cause myocardial infarction, resulting in ventricular dysfunction and sudden death[3,4,9]. Recently, we studied the rheology in the coronary aneurysm by measuring coronary flow velocity and perfusion pressure with a doppler flow guide wire and a pressure-monitoring guide wire. The results of the study suggested that the stagnation of flow and the reduction of shear stress in giant aneurysms could initiate thrombus formation[10]. As a result, sudden death may occur due to acute thrombotic occlusion of the coronary aneurysm. Based on the result of this study, we performed surgical therapy even in young children with Kawasaki coronary disease when myocardial ischemia was detected. We evaluated the preoperative patients' characteristics and the long-term outcome to seek for the optimal time of surgery in patients with Kawasaki coronary disease.

Patients and Methods

From December 1991 to May 2003, twenty-one patients with KD (17 boys and 4 girls ranging in age from 3 to 30 years, mean 12.0 years) had undergone CABG using only arterial grafts in our hospital. The mean age at the time of acute KD was 2.7 years and the mean time range from diagnosis of acute KD to CABG was 8.1 years. In these patients, giant coronary aneurysm (more than 8 mm diameter) located at left main coronary trunk (LMT) in 4 patients, left anterior descending coronary artery (LAD) in 14 patients, right coronary artery (RCA) in 10 patients. The incidences of patient's clinical findings were: preoperative reduced ventricular function in 10 patients (47.6%), old myocardial infarction in 7 patients (33.3%), and valvular dysfunction in 1 patient (4.8%). Operation was performed with standard cardiopulmonary bypass. The internal thoracic artery was used for all patients (17 were to LAD only, 4 were to the diagonal branch and LAD as a sequential graft), whereas the right internal thoracic artery and the right gastroepiploic artery were used for 4 patients. In these 32 grafts, 7 grafts were anastomosed distal to a giant aneurysm without a stenotic region. Aneurysmorrhaphy was performed in 4 patients (LAD 1, RCA 3) as an adjunct procedure. Aneurysmorrhaphy is only indicated for giant aneurysms without a stenotic region with small distal coronary artery unsuitable for bypass grafting to improve the stagnation of flow inside the large aneurysm, except for a patient indicated for a rapidly dilating aneurysm regarded as impending rupture.

A multivariate logistic regression analysis was performed using patient characteristics and difference between the abnormal and normal wall motion in the left ventricle as independent covariates, by selecting a forward-stepping selection method with maximum likelihood estimates and default criteria. The results of analysis showed that the time range from acute KD to CABG was the only predictor for ventricular functional deterioration ($p = 0.03$, odd ratio 1.55, 95%CI: 1.033～2.325). Based on these results, we divided the patients into two groups of short time range (group S, $n = 12$) and the long time range (group L, $n = 9$) in which the mean time range from diagnosis of acute KD to CABG was 3.7 years (range from 1 to 7.7 years) and 13.9 years (range 10～18 years), respectively (**Table 1**). The patients' characteristics of the 2 groups are summarized in **Tables 2** and **3**. In four patients, we could not clarify exactly when

Table 1 Age and time range from diagnosis of acute Kawasaki disease to coronary artery bypass grafting of the two study groups.

	Age of acute KD	Age at operation	Range in years
Group S	3.57 ± 0.69	7.08 ± 0.8	3.73 ± 0.75
Group L	1.62 ± 0.73	18.11 ± 2.3	13.94 ± 1.58
P value	0.12	< 0.01	< 0.01

Data are given as mean ± standard error.
KD = Kawasaki disease; Range in years = time range in years from diagnosis of acute KD to coronary artery bypass grafting

Table 2 Patients' characteristics and operative procedure of short time range group (Group S). The mean time range from diagnosis of acute Kawasaki disease to coronary artery bypass grafting was 3.4 years (range from 1 to 7.7 years).

Case	Gender	Age	Range	Aneurysm	Stenosis	Operative procedure
1	male	3	2.0	LAD *	(−)	LITA-LAD, plication LAD
2	male	3	1.8	LAD, RCA *	# 7	LITA-LAD
3	female	4	1.7	LMT *, RCA	(−)	LITA-LAD
4	male	5	1.0	LAD *, RCA *	(−)	LITA-LAD, plication RCA
5	male	6	1.0	LAD *, RCA *	# 2, # 6	LITA- LAD
6	male	8	2.3	LAD *	# 6	LITA- D_1-LAD
7	male	8	5.1	LMT *, RCA *	# 2, # 6	LITA-LAD, RGEA-RCA
8	male	9	6.5	LAD *	# 6	LITA- D_1-LAD
9	male	9	7.5	LAD, RCA	# 6	LITA-LAD
10	male	9	7.7	LAD *	# 6	LITA-LAD
11	male	10	7.0	LAD *, RCA	# 6	LITA-LAD
12	male	11	2.6	LAD *, RCA *	# 7	LITA-LAD, plication RCA

Aneurysm: = Large aneurysm (maximal diameter > 4mm) * Giant aneurysm (maximal diameter > 8mm), D_1 = first diagonal branch; LAD = left anterior descending coronary artery; LITA = left internal thoracic artery; LMT = left main trunk; Range = time range from diagnosis of acute Kawasaki disease to coronary artery bypass grafting; RCA = right coronary artery; RGEA = right gastroepiploic artery

Table 3 Patients' characteristics and operative procedure in the long time range group (Group L). The mean time range from diagnosis of acute Kawasaki disease to coronary artery bypass grafting was 14.1 years (range 10 ～ 18 years). The exact time of diagnosis as acute KD was unclear in three patients.

Case	Gender	Age	Range	Aneurysm	Stenosis	Operative procedure
13	female	11	10.0	LMT *, RCA *	(−)	LITA- LAD- D_1-Cx, plication RCA
14	male	12	—	LAD, RCA	# 1, # 6	LITA-LAD, RGEA-RCA
15	male	13	12.6	LAD *, RCA *	# 1, # 6	LITA-LAD
16	female	17	16.0	LAD *	# 2, # 7	LITA-LAD, RITA-D_1
17	male	17	12.8	LAD *, RCA *	# 3, # 7	LITA-LAD
18	male	17	—	LAD *, RCA	# 2, # 7	LITA-LAD
19	female	18	18.0	LMT *, RCA *	# 3, # 6 # 9	LITA- D_1-LAD
20	male	29	—	LAD *, RCA *	# 6	LITA- D_1-LAD, RITA-RCA
21	male	30	—	LAD *	# 1, # 11	RGEA-RCA-RITA-Cx

Aneurysm: = Large aneurysm (maximal diameter > 4mm) * Giant aneurysm (maximal diameter > 8mm), Cx = circumflex artery; D_1 = first diagonal branch; LAD = left anterior descending coronary artery; LITA = left internal thoracic artery; RITA = right internal thoracic artery; LMT = left main trunk; Range = time range from diagnosis of acute Kawasaki disease to coronary artery bypass grafting; RCA = right coronary artery; RGEA = right gastroepiploic artery

they were diagnosed as acute KD. However, we classified them in group L, because we could suspect that it takes more than 8 years from diagnosis of acute KD to CABG.

Statistical analysis was performed using SPSS 12.0J (SPSS Inc., Chicago, IL). The non-parametric data were analyzed using the Mann-Whitney U-test to compare values between the two groups. A p value of <0.05 was considered to be significant. All data are presented as the mean ± the standard error of the mean. The event-free curves were constructed by standard non-parametric Kaplan-Meier methods. The data were analyzed using the Log-Rank test to compare values between the two groups.

Results

Preoperative myocardial infarction was documented by the presence of laboratory and/or electrocardiographic change preoperatively in six patients (66.7%) in the group L and only one patient (8.3%) in the group S ($p=0.04$). The incidence of reduced ventricular function were significantly higher in the group L than group S ($p<0.01$) (**Table 4**). There was no significant difference in number of large aneurysms between two groups. There was no surgical mortality or late death in both groups. Angiography was performed in all twenty one patients 1 months to 8 years (mean 2.0 years) postoperatively. The patency rate of the grafts of the group L and group S was 94.1% and 100%, respectively. There was no significant difference in graft patency between the two groups (**Table 5**). The arterial grafts demonstrated good potential for growth as a live conduit in both groups (**Fig. 1**). Moreover, seven giant coronary aneurysms proximal to the graft anastomosis occluded with thrombus formation after CABG without development of myocardial infarction or recurrence of angina (**Fig. 2, A. B**). We performed aneurysmorrhaphy in RCA for three patients. Postoperative coronary flow velocity improved notably and none of the aneurysms showed thrombotic occlusion on postoperative angiogram (**Fig. 3**).

The patients were followed-up from 6 month to 12.2 years (mean 5.0 years) after the operation. One patient in the group L had non-sustained ventricular tachycardia coused by graft occlusion and reoperation was performed one year after CABG, one patient in the group L had a syncopal attack because of advanced AV block 4 years after CABG and one patient in the group L had ventricular tachycardia and an ICD implantation was performed 9 years after CABG. The other 18 patients in both

Table 4 Pre and postoperative cardiac events and status of two study groups.

	Preoperative		Postoperative	
	OMI	asynergy	valvular dysfunction	arrhythmia
Group S	1 (8.3%)	1 (8.3%)	0 (0%)	0 (0%)
Group L	6 (66.7%)	9 (100%)	1 (11.1%)	3 (33.3%)
P value	0.04	0.001	0.43	0.06

OMI = old myocardial infarction

Table 5 Number of large aneurysms, number of grafts and graft patency of two study groups.

	No of large AN	No of grafts	Follow-up	Graft patency
Group S	1.83 ± 0.11	1.25 ± 0.13	4.7 ± 1.14	15/15 (100%)
Group L	1.78 ± 0.15	1.89 ± 0.2	5.49 ± 1.13	16/17 (94.1%)
P value	0.76	0.01	0.81	0.43

Data are given as mean ± standard error.
AN = aneurysm; No = number

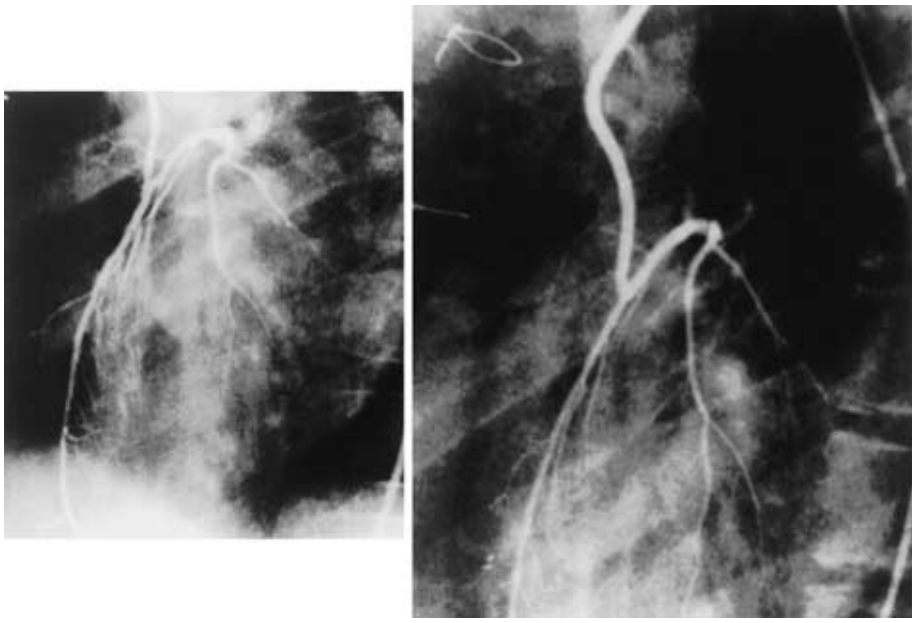

Fig. 1 Postoperative angiogram. One month after (left side) and 6 years after operation (right side). ITA grafts demonstrated good potential for growth and adaptation as a live conduit in both groups and a large aneurysm showed complete degradation.

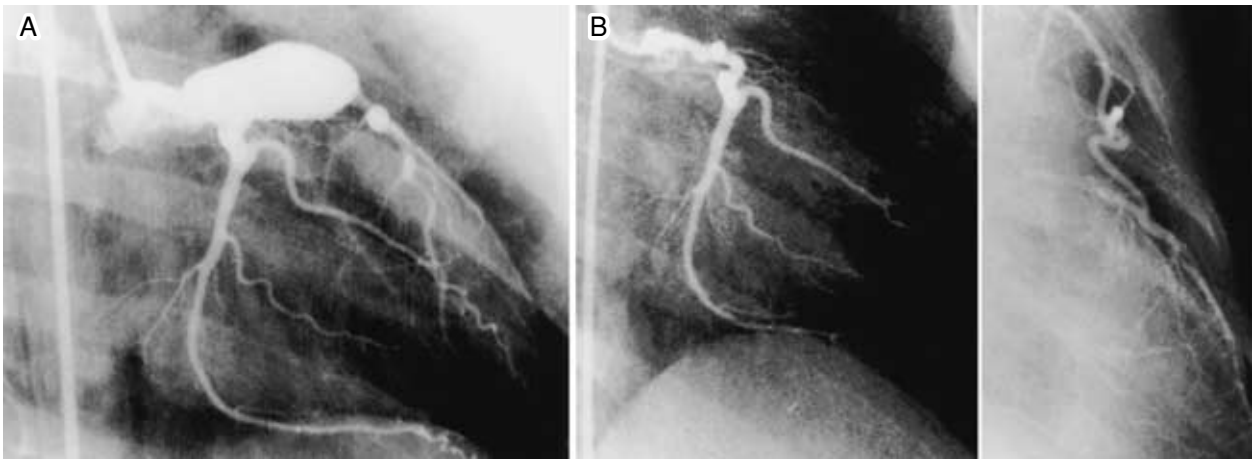

Fig. 2 A Preoperative left coronary angiogram.

Fig. 2 B Native left coronary angiogram (left side) and LITA-LAD graft angiogram (right side) 9 month after operation. Large coronary aneurysm proximal to the anastomosis occluded with thrombus formation without development of myocardial infarction or recurrence of angina.

groups are doing well without any cardiac events or ischemic symptoms. Freedom from cardiac events rate of group L and group S was 66.7% and 100%, respectively during the follow up period 5.5±1.1 years (group L) and 4.7±1.1 years (group S) ($p=0.08$) (**Fig. 4**).

Discussion

The major complication of Kawasaki coronary disease is myocardial infraction caused by thrombus formation inside the giant aneurysm[3]. Kato et al. reported[4] on the long-term consequences of 594 patients sequelae in KD and found giant coronary

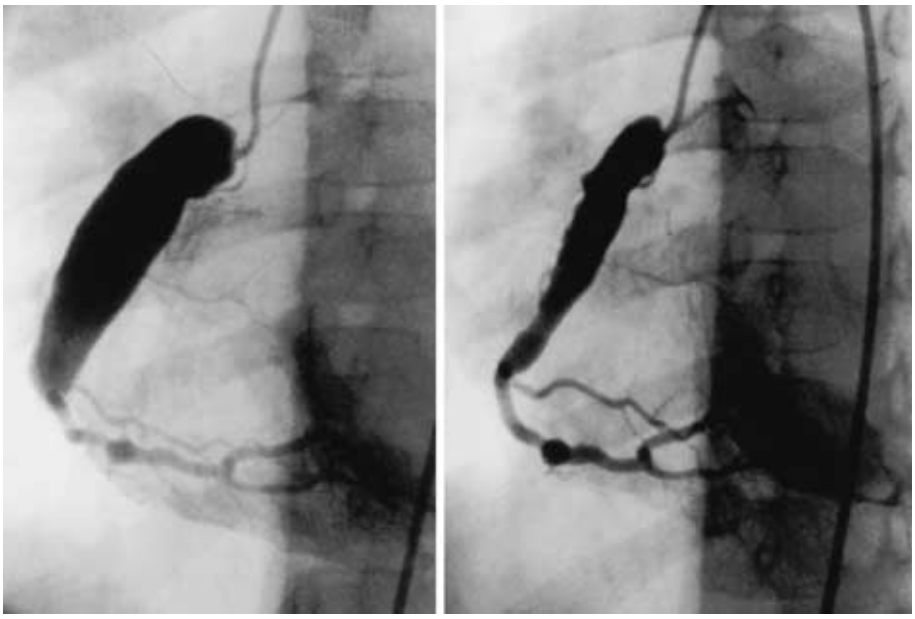

Fig. 3 Aneurysmorrhaphy performed to improve the stagnation of flow inside the aneurysm. Preoperative average peak velocity was 15 cm/sec and coronary flow ratio was 1.2 (left side) . Postoperative average peak velocity was 22 cm/sec and coronary flow ratio was 2.5 (right side).

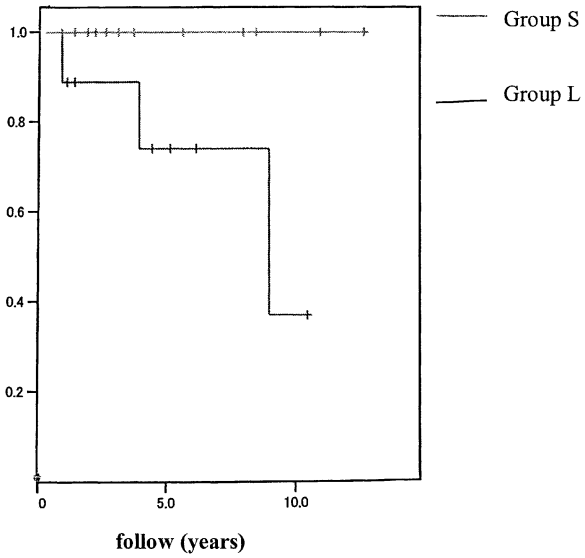

Fig. 4 Postoperative actuarial freedom from cardiac events rate of group L and group S was 66.7% and 100%, respectively during the follow up period 5.5±1.1 (group L) and 4.7 ±1.1 (group S) (p=0.08).

aneurysms (4 or more times normal, or >8 mm in internal diameter) at the first coronary angiogram in 26 patients (4.4%). Twelve of these progressed to stenosis or obstruction of the coronary artery, myocardial infarction occurred in 8 of these 12 patients and 4 of these 8 died. Tatara et al. reported on the incidence of coronary obstruction subsequent to giant aneurysms with a maximal diameter>8 mm in 25 aneurysms among 20 patients. Coronary obstruction occurred in six cases (30%)[9]. One of these patients developed symptomatic myocardial infarction and two developed silent myocardial infarction. In five cases, a persistent perfusion defect was found by myocardial imaging. They conclude that giant aneurysms are likely to progress and become obstructive within a few years even if antiplatelet therapy is given.

In 1973 Kitamura et al reported CABG with autologous saphenous vein grafts in children and adolescents with KD for the first time[11]. Since then, myocardial revascularization for Kawasaki coronary lesions has been conducted increasingly[12,13]. Subsequent follow-up revealed that saphenous vein grafts frequently become obstructed within 1 to 2 years[14]. Internal mammary artery has been used for pediatric CABG for significant coronary obstructive lesions in patient with KD[15] or congenital atresia of the left coronary artery[16,17] with excellent patency rate. It also has growth potential to adapt a ptients' growth as a live conduit[18]. A study of the long-term

outcome of myocardial revascularization in patients with KD showed a significantly higher survival in the ITA group than saphenous vein group[6].

Kato et al. analyzed clinical data from 195 patients with myocardial infarction complicating KD[3]. The myocardial infarction usually occurred within the first year of illness, but 27.2% of the patients had myocardial infarction more than 1 year later, 22% of the patients died during the first attack, 16% of the survivors had a second attack, and 43% of all the survivors are doing well; however, others have some type of cardiac dysfunction, such as mitral regurgitation, decreased ejection fraction of the ventricle, or left ventricular aneurysm. Checchia et al. reported[19] that 13 KD patients who underwent cardiac transplantation suffered from irreversible severe myocardial dysfunction and ventricular arrhythmia. Eight patients underwent coronary artery angiography before transplant, and all had evidence of aneurysmal dilatation and/or stenosis causing obstruction. Four patients had undergone CABG before the transplantation, but the ventricular function did not improve after surgery and all were transplanted within 1 year postoperatively.

One of remarkable finding regarding coronary lesions of KD was the apparent regression of aneurysms[20]. In half of patients, coronary aneurysms show regression on angiography during the first 6 months to 2 years after the acute KD. Some of whom documented neither obstruction or stenosis nor irregularity of arterial wall on follow up angiography. These data suggested that in patients with large aneurysms during infancy or 2 year after acute KD careful follow-up with anticoagulant therapy would be a reasonable strategy. However, even in these follow-up periods, when the myocardial ischemia caused by thrombus formation inside the giant aneurysm is evident, we recommend the surgical therapy as soon as possible.

In conclusion, we successfully applied surgical therapy for Kawasaki coronary disease. Based on our experience, surgical therapy in a short interval from diagnosis of acute KD to CABG appears to offer a better prognosis in terms of establishing a good quality of life.

References

1. Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa H: A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. Pediatrics 1974; 54: 271–276.
2. Nakano H, Ueda K, Saito A, Nojima K: Repeated quantitative angiograms in coronary arterial aneurysm in Kawasaki disease. Am J Cardiol 1985; 56: 846–851.
3. Kato H, Ichinose E, Kawasaki T: Myocardial infarction in Kawasaki disease: Clinical analyses in 195 cases. J Pediatr 1986; 108: 923–927.
4. Kato H, Sugimura T, Akagi T, Sato N, Hashino K, Maeno Y, Kazue T, Eto G, Yamakawa R: Long-term consequences of Kawasaki disease A 10- to 21-year follow-up study of 594 patients. Circulation 1996; 94: 1379–1385.
5. Fujiwara H, Hamashima Y: Pathology of the heart in Kawasaki disease. Pediatrics 1978; 61: 100–107.
6. Kitamura S, Kameda Y, Seki T, Kawachi K, Endo M, Takeuchi Y, Kawasaki T, Kawashima Y: Long-term outcome of myocardial revascularization in patients with Kawasaki coronary artery disease: A multicenter cooperative study. J Thorac Cardiovasc Surg 1994; 107: 663–674.
7. Ogawa S, Fukazawa R, Ohkubo T, Zhang J, Takeuchi N, Kuramochi Y, Hino Y, Jimbo O, Katube Y, Kamisago M, Genma Y, Yamamoto M: Silent myocardial ischemia in Kawasaki disease: Evaluation of percutaneous transluminal coronary angioplasty by dobutamine stress testing. Circulation 1997; 96: 3384–3389.
8. Ito T, Akimoto K, Ohkubo M, Nishimoto K, Yabuta K, Takaya J, Yamaguchi H: Application of percutaneous transluminal coronary angioplasty to coronary arterial stenosis in Kawasaki disease. Circulation 1996; 93: 1709–1715.
9. Tatara K, Kusakawa S: Long-term prognosis of giant coronary aneurysm in Kawasaki disease: An angiographic study. J Pediatr 1987; 111: 705–710.
10. Kuramochi Y, Ohkubo T, Takechi N, Fukumi D, Uchikoba Y, Ogawa S: Hemodynamic factors of thrombus formation in coronary aneurysms associated with Kawasaki disease. Pediatrics International 2000; 42: 470–475.
11. Kitamura S, Kawashima Y, Miyamoto K, Kobayashi T, Matsuda H, Ohgitani N, Kodama K, Minamino T, Manabe H: Multiple coronary aneurysms resulting in myocardial infarction in a young man. J Thorac Cardiovasc Surg 1973; 70: 290–297.
12. Kitamura S, Kawashima Y, Fujita T, Mori T, Oyama C, Fujino M, Kozuka T, Nishizaki K, Manabe H: Aortocoronary bypass grafting in a child with coronary artery obstruction due to mucocutaneous lymph node syndrome. Circulation 1976; 53: 1035–1040.
13. Sandiford FM, Vargo TA, Shih JY, Pelargonio S, McNamara DG: Successful Triple coronary artery

bypass in a child with multiple coronary aneurysms due to Kawasaki's disease. J Thorac Cardiovasc Surg 1980; 79: 283–287.
14. Suma K, Takeuchi Y, Shiroma K, Tsuji T, Inoue K, Yoshikawa T, Kayama Y, Narumi J, Asai T, Kusakawa S: Early and late postoperative studies in coronary arterial lesions resulting from Kawasaki's disease in children. J Thorac Cardiovasc Surg 1982; 84: 224–229.
15. Kitamura S, Kawachi K, Seki T, Morita R, Nishii T, Mizuguchi K, Fukutomi M, Hamada Y, Iioka S: Bilateral internal mammary artery grafts for coronary artery bypass operations in children. J Thorac Cardiovasc Surg 1990; 99: 708–715.
16. Cooley DA, McNamara DG, Duncan JM, Ott DA: Internal mammary-anomalous left anterior descending coronary artery graft in 16-month-old infant with tetralogy of Fallot: 30-month follow-up. Ann Thorac Surg 1980; 30: 588–591.
17. Fortune RL, Baron PJ, Fitzgerald JW: Atresia of the left main coronary artery: Repair with left internal mammary artery bypass. J Thorac Cardiovasc Surg 1987; 1 : 150–151.
18. Kitamura S, Seki T, Kawachi K, Morita R, Kawata T, Mizuguchi K, Kobayashi S, Fukutomi M, Nishii T, Kobayashi H, Oyama C: Excellent patency and growth potential of internal mammary artery grafts in pediatric coronary artery bypass surgery. Circulation 1988; 78 (suppl I): I–129–139.
19. Checchia PA, Pahl E, Shaddy RE, Shulman ST: Cardiac transplantation for Kawasaki disease. Pediatrics 1997; 100: 695–699.
20. Kato H, Ichinose E, Yoshioka F, Takechi T, Matsunaga S, Suzuki K, Rikitake N: Fate of coronary aneurysms in Kawasaki disease. Serial coronary angiography and long-term follow-up study. Am J Cardiol 1982; 49: 1758–1766.

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