

data suggest that the BK_{Ca} channels are not involved in O₂-induced ductal constriction, endogenous factors such as 17 β -estradiol [31] and epoxyeicosatrienoic acids [32], which are known to be BK_{Ca} activators, may be involved in the regulation of DA tone in fetuses. In addition, the present data suggest that the BK_{Ca} activator has the potential to maintain the patency of DA after birth, which may benefit patients suffering from ductus-dependent congenital heart defects. The progressive remodeling and reconstruction of NB DA [5] may account for the dramatic abatement of BK_{Ca} channels (Figs. 1, 2, 4). Further studies are needed to understand the in vivo effects of BK_{Ca} activators and the DA remodeling process after birth.

In conclusion, BK_{Ca} channels are present in the DAs of premature and mature rat fetuses, as well as newborns. They are relatively abundant in the mature DA. Although BK_{Ca} channels are not involved in O₂-induced ductal constriction, BK_{Ca} activators may possibly have the potential to maintain the patency of ductus after birth.

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Stenting in Congenital Heart Disease – Medium- and Long-Term Outcomes From the JPIC Stent Survey –

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Background: Medium- and long-term efficacy of intravascular stenting for congenital heart disease (CHD) has not been determined in Japan.

Methods and Results: The study comprised a retrospective survey of Palmaz or Palmaz Genesis stent implantation for pulmonary artery stenosis (PA), aortic coarctation, and superior and inferior vena cava lesions (SIVC) from May 1995 to February 2009, occurring in association with pre- or postoperative CHD at 14 leading hospitals. Stents were implanted in 255 patients with 312 lesions (PA, 253 lesions in 199 patients; aorta, 38 lesions in 35 patients; SIVC, 21 lesions in 21 patients). Age at the initial stenting was median 10 years, and the follow-up interval ranged from 6 to 144 months. The minimum lumen diameter (MLD) of the PA, aorta, and SIVC was increased from 4.7 ± 2.1 , 6.6 ± 2.3 , and 4.4 ± 2.2 mm to 8.8 ± 2.7 , 12.0 ± 3.8 , and 9.2 ± 2.6 mm, respectively ($P<0.01$). Cumulative freedom from redilation was 84% at 72 months, 95% at 54 months, and 81% at 50 months, for the PA, aorta, and SIVC, respectively. In 187 redilations, the MLD of the PA, aorta, and SIVC increased from 6.1 ± 2.5 , 7.9 ± 2.9 , and 5.3 ± 2.4 mm, to 8.3 ± 2.7 , 9.8 ± 3.5 , and 7.3 ± 1.9 mm, respectively ($P<0.01$). There were no deaths associated with stent implantation.

Conclusions: Percutaneous stenting using Palmaz or Palmaz Genesis stents and redilation are now common procedures in Japan with little morbidity during the medium- and long-term follow-up period. (*Circ J* 2010; **74**: 1676–1683)

Key Words: Catheterization; Congenital heart disease; Redilation; Stents

Stent implantation has become an essential treatment strategy for stenosis of the great vessels associated with various congenital heart diseases (CHDs). There have been several reports from Japan on the acute and medium-term outcomes of stenting, but each report concerned limited number of patients because each Japanese center had performed stenting only a small number of times.^{1–4} Furthermore, there are no reports of the long-term outcome beyond 10 years after stenting.

Consequently, the Japanese society of Pediatric Interventional Cardiology (JPIC) undertook a questionnaire survey on stenting for great vessel stenosis associated with CHDs.

Methods

Based on a preliminary survey by committee members of the JPIC, we selected 16 hospitals that had stented more than 10 patients for stenosis of the great vessels associated with

CHDs, and retrospective questionnaires on stenting using either an original Palmaz or Palmaz Genesis stent (Cordis, Johnson & Johnson, Miami, FL, USA) were sent to each of these hospitals.

The questionnaires requested information about underlying CHDs, age at stenting, follow-up interval, stent type used and balloon (if remounted), minimal lumen diameter (MLD), lesion length, diameter of the reference vessel, peak-to-peak (in pulmonary stenosis and coarctation) or mean (in venous stenosis) pressure gradient before and after stenting, and over the entire follow-up interval, reasons for and outcomes of redilations, surgical interventions to stented vessels, and adverse events either with stenting or redilations.

The background data of patients were analyzed by Tukey's or Steel-Dwass's multiple comparisons, the acute effects of stenting were compared by paired t-test, and the percent changes in MLD and pressure gradients by t-test. The MLD and pressure gradients over the entire follow-up period were

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Table 1. Background Data of the Patients				
	PS	CoA	SIVC	P value
No. of patients	199	35	21	
No. of lesions	253	38	21	
No. of sessions	225	36	21	
Age, Min/Med/Max (years)	0/11/56	0/14/31	0/7/39	<0.05 ¹
≤1	7	2	4	
1–6	46	1	2	
6–10	40	2	7	
10–15	65	13	3	
≥15 years	39	17	4	
Unidentified	2	0	1	
Follow-up (months)				
Min/Med/Max	6/24/144	6/24/120	6/18/84	
Sex				
M/F/Unidentified	108/90/1	16/19/0	9/11/1	NS
Underlying heart disease				
TF	74	0	0	
PA/VSD	37	0	6	
UVH	28	0	4	
TGA	17	0	3	
DORV	9	0	2	
Truncus	9	0	0	
VSD	4	0	0	
PA/IVS	2	0	0	
po AS (Ross)	2	0	0	
CoA complex (after PAB)	2	0	0	
PAPVC	0	0	4	
CoA complex	0	26	1	
TAPVC	0	0	1	
Other	11	0	0	
None	3	8	0	
Unidentified	1	1	0	
Purpose of stenting				
Primary option	116	30	16	<0.01 ¹
Secondary option	85	5	3	<0.05 ²
Other	49	3	1	NS ³
Unidentified	3	0	1	
Stent type				
Palmaz medium	46	2	5	NS
Palmaz large	199	34	13	
Palmaz extra-large	10	6	1	
Palmaz (unidentified)	9	0	1	
Genesis medium on Slalom	9	0	1	
Genesis large	14	0	0	
Genesis (unidentified)	1	0	0	
No. of stents implanted per lesion				
Min/Med/Max	1/1/5	1/1/4	1/1/1	

¹PS vs CoA; ²PS vs SIVC; ³CoA vs SIVC.

PS, pulmonary stenosis; CoA, coarctation of aorta; SIVC, superior or inferior vena cava; Min, minimum; Med, median; Max, maximum; NS, not significant; TF, tetralogy of Fallot; PA/VSD, pulmonary atresia (PA) with ventricular septal defect (VSD); UVH, univentricular heart; TGA, transposition of great arteries; DORV, double outlet right ventricle; Truncus, truncus arteriosus; PA/IVS, PA with intact ventricular septum; AS, aortic stenosis; PAPVC, partial anomalous pulmonary venous connection; TAPVC, total anomalous pulmonary venous connection.

also analyzed, and we used the Kaplan-Meier method to calculate freedom from re-intervention following restenosis. Percent changes in MLD and pressure gradient were defined as [(MLD after-before)/MLD before]×100, and [(pressure gradient before -after)/pressure gradient before]×100, and we used

multiple stepwise regression analysis to identify factors that might contribute to these changes in stenting and in the initial redilation. For parameters that might have contributed to freedom from re-intervention following restenosis or to adverse events, we used stepwise multiple logistic regression analysis.

	Before stenting						After stenting						P value
	n	Mean	SD	Min	Med	Max	n	Mean	SD	Min	Med	Max	
All													
MLD	260	5.0	2.3	0.9	4.8	12.0	260	9.3	3.1	3.4	9.2	20.4	<0.01
PG	210	28	21	0	23	108	210	11	12	0	7	60	<0.01
PS													
MLD	205	4.7	2.1	1.0	4.5	12.0	205	8.8	2.7	3.4	8.9	15.0	<0.01
PG	162	30	22	0	24	108	162	12	12	0	10	60	<0.01
CoA													
MLD	37	6.6	2.3	1.7	6.9	10.5	37	12.0	3.8	4.4	12.0	20.4	<0.01
PG	32	27	13	10	24	57	32	8	12	0	5	50	<0.01
SIVC													
MLD	18	4.4	2.2	0.9	4.5	7.5	18	9.2	2.6	4.0	9.9	12.0	<0.01
PG	16	7	4	2	7	14	16	1	1	0	1	4	<0.01

MLD, minimum lumen diameter; PG, pressure gradient; n, number of lesions; SD, standard deviation; PS, pulmonary stenosis. Other abbreviations see in Table 1.

	% change in MLD			% change in PG		
	Slope	P value	R ²	Slope	P value	R ²
Age	2.2	<0.01		–	NS	
PS	–	NS		–20.9	<0.01	
CoA	–	NS		–	NS	
SIVC	–	NS	0.42	–	NS	0.08
Palmaz large + Extra	–	NS		–	NS	
Medium + Genesis	–	NS		–	NS	
MLD before stenting	–26.7	<0.01		–	NS	
PG before stenting	0.6	<0.05		–	NS	
Lesion length	–	NS		–	NS	

Abbreviations see in Tables 1,2.

A predictive value less than 0.05 was taken as statistically significant.

Results

Of the 16 hospitals, 14 replied to the questionnaires. The respective number of patients, lesions, and sessions of stenting were 199, 253, and 225 with pulmonary stenosis; 35, 38, and 36 for coarctation; and 21, 21 and 21 for vena cava stenosis.

Background Data of the Patients (Table 1)

Age at Stenting Age at stenting ranged from 0 to 56 (median 11) years for pulmonary stenosis, 0–31 (14) years for coarctation, and 0–39 (7) years for stenosis of the vena cava. Age at stenting for coarctation was significantly older than for pulmonary stenosis ($P<0.05$).

Follow-up Interval Follow-up intervals ranged from 0.5 to 12 (median 2) years for pulmonary stenosis, 0.5–10 (2) years for coarctation, and 0.5–7 (1.5) years for stenosis of vena cava. There were 3 and 2 patients with pulmonary stenosis and coarctation, respectively, whose follow-up intervals were longer than 10 years, and the longest follow-up interval for vena cava stenosis was 8 years for 2 patients.

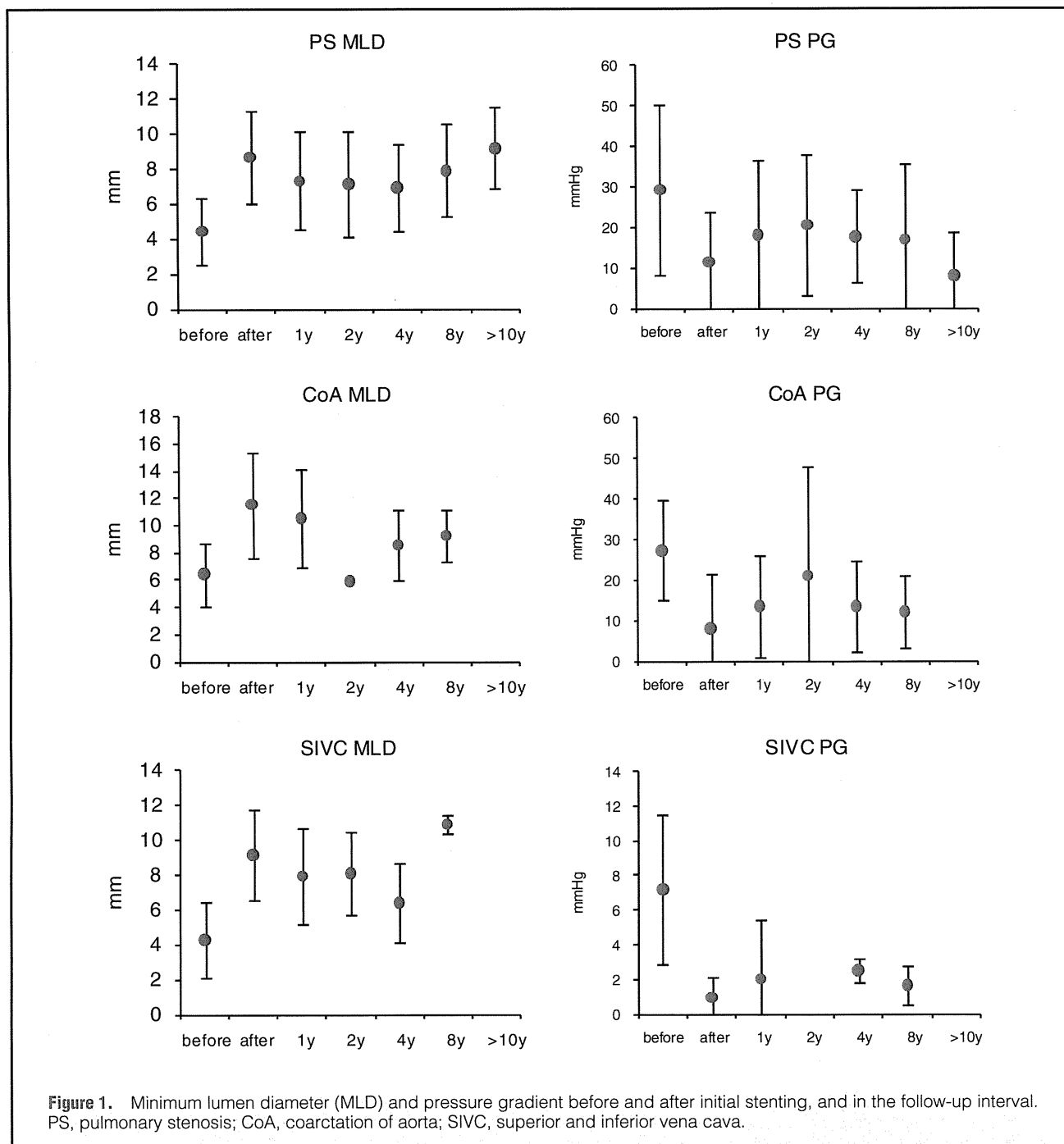
Sex The sex distribution in pulmonary stenosis, coarctation, and vena cava stenosis was 108/90/1 (male/female/unknown), 16/19/0, and 9/11/1, respectively. There was no significant difference among the 3 groups.

Underlying Heart Diseases In the pulmonary stenosis group, tetralogy of Fallot was the most common underlying heart disease, and pulmonary atresia with ventricular septal defect, transposition of great vessels, and univentricular heart were also frequent underlying lesions. In the aortic coarctation group, 26 patients had complex coarctation, 8 were simple and 1 was unknown. For stenosis of the vena cava, pulmonary atresia with ventricular septal defect, partial anomalous pulmonary venous connection, and univentricular heart were common underlying lesions.

Goal of Stenting For pulmonary stenosis, stenting was the primary option in approximately two-thirds of cases, and a secondary option was to repeat the previous treatment, which was mostly simple balloon angioplasty, in one-third of the patients. For coarctation ($P<0.01$) and stenosis of the vena cava ($P<0.05$), the primary option was more frequently performed than in pulmonary stenosis cases.

Stent Type The original Palmaz large stent was the most commonly implanted stent for all lesions, while a small number of Palmaz medium, and extra-large stents were used. A small number of Palmaz Genesis stents (medium on Slalom and large) were implanted in pulmonary stenosis and vena cava stenosis. There was no significant difference in specifications of stent among the 3 groups.

Number of Stents Implanted The number of stents implanted per lesion ranged from 1 to 5 (median 1) in pulmonary stenosis, 1–4 (1) in coarctation, and only 1 stent



was implanted in all the vena cava lesions.

Acute Outcome of Stenting

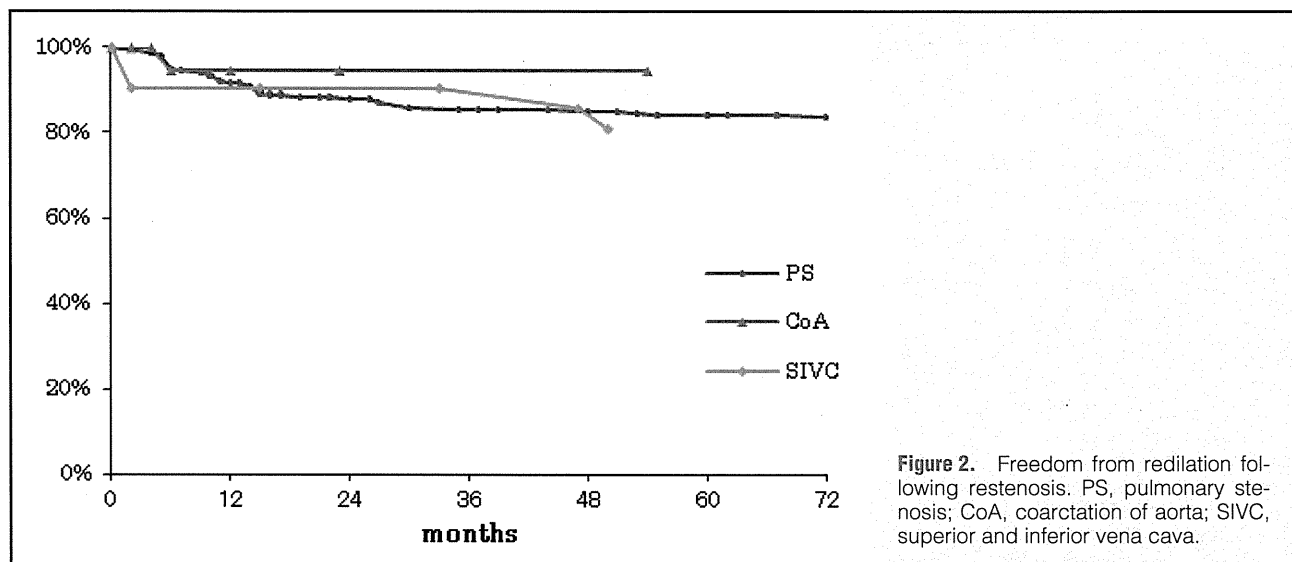
MLD and the pressure gradient before and after stenting could be analyzed in 260 and 210 lesions, respectively. MLD increased from 5.0±2.3 (mean±standard deviation, range, 0.9–12.0) mm before stenting to 9.3±3.1 (3.4–20.4) mm after stenting, and the pressure gradient decreased from 28±21 (0–108) mmHg to 11±12 (0–60) mmHg (P<0.01, Table 2).

Pulmonary Stenosis MLD and the pressure gradient before and after stenting could be analyzed in 205 and 162 lesions, respectively. The MLD increased from 4.7±2.1 (1.0–12.0) mm to 8.8±2.7 (3.4–15.0) mm, and the pressure gra-

dient decreased from 30±22 (0–108) mmHg to 12±12 (0–60) mmHg (P<0.01, Table 2).

Coarctation MLD and the pressure gradient before and after stenting could be analyzed in 37 and 32 lesions, respectively. MLD increased from 6.6±2.3 (1.7–10.5) mm to 12.0±3.8 (4.4–20.4) mm, and the pressure gradient decreased from 27±13 (10–57) mmHg to 8±12 (0–50) mmHg (P<0.01, Table 2).

Vena Cava Stenosis MLD and the pressure gradient before and after stenting could be analyzed in 18 and 16 lesions, respectively. MLD increased from 4.4±2.2 (0.9–7.5) mm to 9.2±2.6 (4.0–12.0) mm, and the pressure gradient decreased from 7±4 (2–14) mmHg to 1±1 (0–4) mmHg (P<0.01, Table 2).



	Before					After					P value
	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max	
All											
MLD	154	6.2	2.6	0.9	14.4	154	8.4	2.7	3.4	17.8	<0.01
PG	140	24	16	0	77	140	13	11	0	64	<0.01
PS											
MLD	137	6.1	2.5	0.9	14.4	137	8.3	2.7	3.4	17.8	<0.01
PG	125	24	16	0	77	125	14	11	0	64	<0.01
CoA											
MLD	11	7.9	2.9	4.4	12.1	11	9.8	3.5	4.8	16.5	<0.01
PG	10	23	11	5	40	10	10	7	0	18	<0.01
SIVC											
MLD	6	5.3	2.4	1.7	8.7	6	7.3	1.9	5.6	10.5	<0.01
PG	5	4	6	0	14	5	2	2	0	5	NS

Abbreviations see in Tables 1,2.

Factors Contributing to Percent Changes in MLD and Pressure Gradient at Initial Stenting

We analyzed whether age at stenting, site of the lesion, type of stent (Palmaz large+extra large vs Palmaz medium+Genesis), and MLD/pressure gradient/lesion length before stenting might contribute to the percent changes in MLD and pressure gradient at stenting.

Percent changes in MLD positively correlated with age at stenting and pressure gradient before stenting, while negatively correlating with MLD before stenting. Percent changes in pressure gradients in pulmonary stenosis were significantly smaller than in coarctation and vena cava stenosis (Table 3).

Long-Term Prognosis

Late Prognosis of MLD and Pressure Gradient In the follow-up period, 187 redilations were performed following either size-mismatch or in-stent stenosis; however, there was no significant difference in MLD or pressure gradient between just after stenting and in the follow-up period. Consequently, the benefit of stenting was preserved in the late follow-up period (Figure 1).

Freedom From Re-Intervention In pulmonary stenosis, freedom from re-intervention gradually decreased to 92%

at 12 months and 88% at 24 months, but beyond 60 months there was a plateau (ie, 84% at both 60 and 72 months). In coarctation, it was 95% at 12 months, with no further decrease at 24 and 54 months. In vena cava stenosis, it gradually decreased over time to 81% at 50 months. However, there was no significant difference in freedom from re-intervention at 12 and 48 months, or the entire follow-up interval among the 3 groups (Figure 2). We analyzed for the same potential influences on freedom from re-intervention as previously listed. A small MLD before stenting was the only risk factor for poor freedom from re-intervention at any period (at 12 months: $P<0.05$, odds ratio (OR) 0.74, 95% confidence interval (CI) 0.57–0.95; at 48 months: $P<0.01$, OR 0.72, 95%CI 0.57–0.91; for the entire follow-up interval: $P<0.01$, OR 0.73, 95%CI 0.58–0.92).

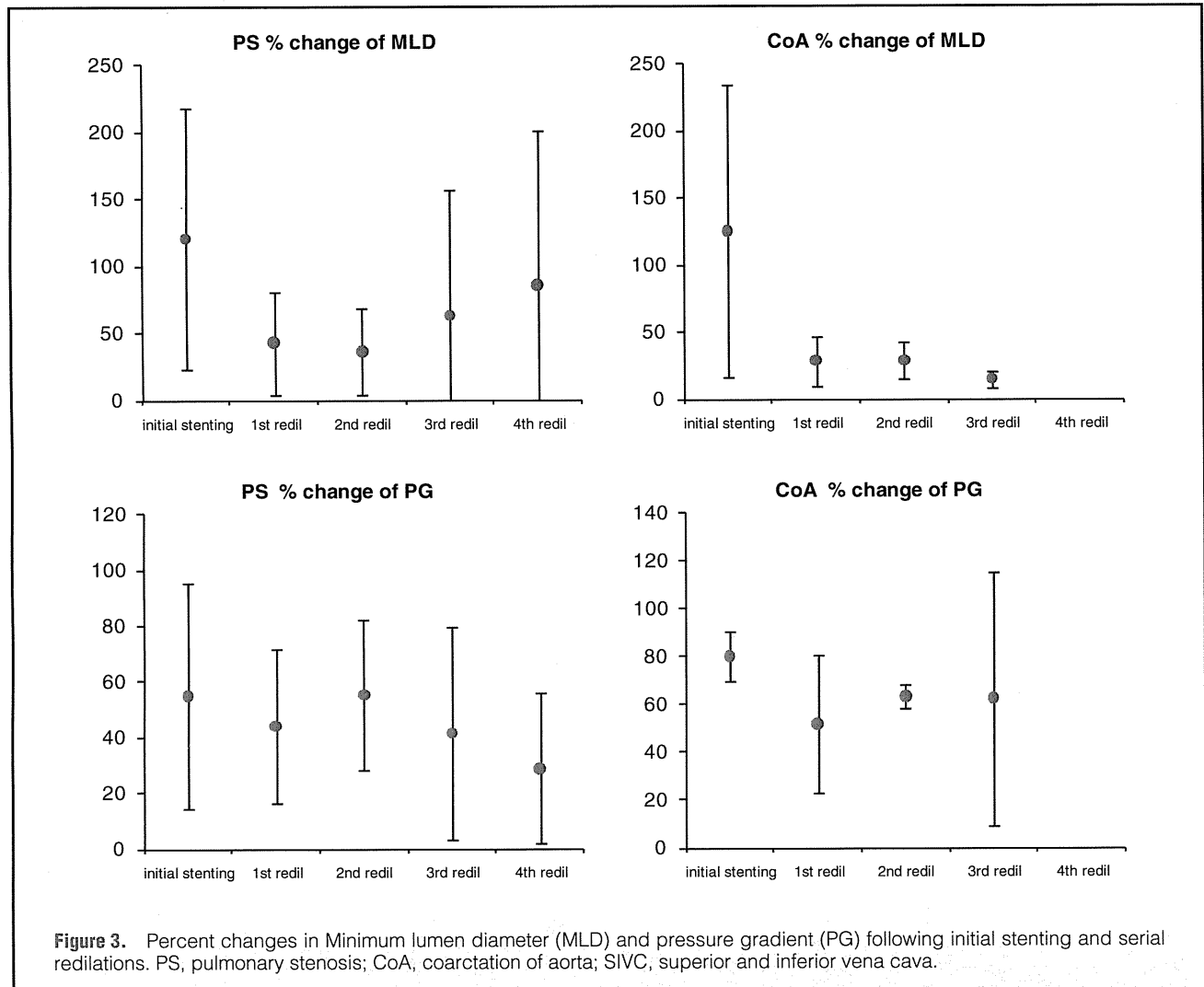
Redilation

Efficacy of Redilation Redilations were performed 187 times in 108 patients, and the MLD and pressure gradient both before and after redilation could be analyzed in 154 and 140 sessions, respectively.

In all redilations, MLD increased from 6.2 ± 2.6 (0.9–14.4) mm to 8.4 ± 2.7 (3.4–17.8) mm ($P<0.01$), and the pressure

	Initial stenting					Redilation					P value
	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max	
MLD	260	111	87	0	539	154	50	76	0	756	<0.01
PG	204	63	33	-100	100	134	48	28	-17	100	<0.01

Abbreviations see in Tables 1,2.



gradient decreased from 24 ± 16 (0–77) mmHg to 13 ± 11 (0–64) mmHg ($P < 0.01$, Table 4).

In pulmonary stenosis, 157 redilations, which included 1–5 times in 107, 29, 10, 7, and 4 lesions each, were performed. MLD and the pressure gradient both before and after redilation could be analyzed in 137 and 125 lesions, respectively. MLD increased from 6.1 ± 2.5 (0.9–14.4) mm to 8.3 ± 2.7 (3.4–17.8) mm ($P < 0.01$), and the pressure gradient decreased from 24 ± 16 (0–77) mmHg to 14 ± 11 (0–64) mmHg ($P < 0.01$, Table 4).

For coarctation, 22 redilations, which included 1–3 redilations in 13, 6, and 3 lesions each, were reported. MLD and the pressure gradient both before and after redilation could be analyzed in 11 and 10 lesions, respectively. MLD increased from 7.9 ± 2.9 (4.4–12.1) mm to 9.8 ± 3.5 (4.8–16.5) mm ($P < 0.01$), and the pressure gradient decreased from 23 ± 11 (5–

40) mmHg to 10 ± 7 (0–18) mmHg ($P < 0.01$, Table 4).

In vena cava stenosis, 1 redilation was performed in 8 lesions, and MLD and pressure gradient both before and after redilation could be analyzed in 6 and 5 lesions, respectively. MLD increased from 5.3 ± 2.4 (1.7–8.7) mm to 7.3 ± 1.9 (5.6–10.5) mm ($P < 0.01$, Table 4). Although the pressure gradient decreased from 4 ± 6 (0–14) mmHg to 2 ± 2 (0–5) mmHg, it was not statistically significant.

Percent Changes in MLD and Pressure Gradient in Redilations Percent changes in MLD and pressure gradient in the initial stenting were 111 ± 87 ($n=260$, 0–539) and 63 ± 33 ($n=204$, -100–100) %, respectively, both of which were significantly larger than for redilation, these being 50 ± 76 ($n=154$, 0–756) % and 48 ± 28 ($n=134$, -17–100) %, respectively ($P < 0.01$, Table 5).

In pulmonary stenosis and coarctation cases in which multiple redilations were performed, we analyzed the percent changes for each redilation. Percent changes in MLD and pressure gradient in the initial stenting were significantly larger than those in the first redilation; however, the percent changes for each redilation were comparable. Consequently, the efficacy of redilation was preserved, even after multiple redilations (Figure 3).

Factors Contributing to Percent Changes in MLD and Pressure Gradient at Initial Redilation We analyzed whether any of the factors previously listed might contribute to the percent changes in MLD and pressure gradient following redilation.

Percent changes in MLD positively correlated with age at stenting ($P < 0.01$, slope 1.5), and negatively correlated with MLD before the redilation ($P < 0.01$, slope -7.5), significantly but weakly ($R^2 = 0.10$). However, we did not identify any factors that contributed to the percent changes in pressure gradient.

Adverse Events

There were 80 events (28.4% of all sessions) in 59 patients (23.1% of all patients). Surgical treatment was required for 8 events (2.8% of all sessions) in 8 patients (2.8% of all patients).

Pulmonary Stenosis There were 67 events in 46 patients. Stent fracture occurred 8 times in 7 patients, of which 2 were associated with the procedure at initial stenting or redilation. Otherwise, 6 events were judged as caused by metal fatigue. Six fractured stents, including 1 that was procedure-related, were original Palmaz, and 2 were Palmaz Genesis, 1 being procedure-related. Fractured stents were retrieved surgically in 2 patients, and additional stenting was carried out as a bail-out procedure in 3 patients. The other 2 patients did not require any treatment, as there was no hemodynamic compromise following fracture of the stent. Stent fracture caused by metal fatigue was detected at 3, 7, 11, 37, 62, 67 months, respectively, after stenting.

Other adverse events included 23 inappropriately positioned stents (16 stent migrations during stent deployment, 5 slippages of stent from the balloon, others 2), 17 balloon ruptures, 6 incidents of late stent migration, 2 each of trouble in removing the catheter, lung congestion, and rupture of the Berman catheter, and 1 each of stent migration at redilation, deformation of the stent, difficulty in removing the balloon catheter, gastrointestinal bleeding, paralysis of the brachial plexus, perforation of the pulmonary artery, and hemoptysis. Late stent migration was detected the day after stenting in 2 cases, at 4 months after stenting in 2, and in 1 case each at 5 and 14 months after stenting. The stent was retrieved surgically in 3 cases of inappropriate stent position, and 2 of late stent migration.

There were 14 adverse events in 13 patients at late redilation: 9 balloon ruptures in 9 patients, and 1 each of hemoptysis, stent fracture, stent migration, and difficulty in removing of the balloon catheter or the Berman catheter. A stent was removed surgically in 1 patient because of stent fracture.

Coarctation There were 10 events in 10 patients: 7 balloon ruptures, and 1 case each of severe damage to the femoral artery, which was surgically repaired, retroperitoneal bleeding and transient AV block. Most events occurred at the initial stenting, except for a balloon rupture complicating redilation 36 months after stenting.

Vena Cava Stenosis One case each of hypotension, sick sinus syndrome, and tachyarrhythmia occurred in 3 patients.

Factors Contributing to Procedure-Related Complications

We analyzed whether any procedure-related factors, such as age at stenting, site of the lesion, type of stent (Palmaz large+extra large vs Palmaz medium+Genesis), MLD/pressure gradient/lesion length before stenting, contributed to the occurrence of adverse events.

Only a large pressure gradient before stenting was a weak but significant risk factor for adverse events ($P < 0.05$; OR, 1.02; 95%CI, 1.00–1.04).

Excluding 2 stent fractures, adverse events were complicated by stenting with the Palmaz stent.

Discussion

From the data compiled by the investigation committee of the JPIC, 83 cases of stenting of lesions other than coronary arteries and redilations in 52 patients were reported in 2008. Most target lesions in this report were either pulmonary stenosis or aortic coarctation, although stenting of the ductus arteriosus has been reported.⁵ Although several reports from North America and Europe describe medium- and long-term outcomes and redilation following stent implantation in CHDs, the longest follow-up ranges from 5 to 6 years.^{6–8} Only a few reports based on limited number of patients describing prognosis beyond 10 years exist. Japanese reports are few and cover the medium-term outcome in a small number of patients.^{2,3}

As reported in many previous series,^{9–16} the acute outcome of stenting was quite effective in this survey, too. Age at stenting and the pressure gradient before stenting were positive factors that determined the percent change in MLD by stenting, whereas the MLD at stenting was a negative factor. Furthermore, the percent changes in pressure gradient in the pulmonary stenosis patients were significantly smaller than in those with coarctation or vena cava stenosis. These issues may be expected, as the efficacy of stenting is partly affected by age and constitution, and in pulmonary stenosis, the pressure gradient alone does not always determine the severity of the stenosis.

Comprehensive investigation is indispensable regarding the efficacy of redilation, which may be scheduled to overcome either a size-mismatch associated with somatic growth or in-stent restenosis, as stenting involves permanently implanting metal stent in the great vessels of growing children. There have been several reports from Western countries on this point,^{7,8,17–19} but, in Japan, few studies have addressed this issue. The longest follow-up interval in our survey was 12 years, and a considerable number of patients underwent redilations. Repetitive redilations in some patients were as effective as the initial redilation. Although indications for redilation were not uniform among facilities, repetitive redilations definitely were as effective, and retained their efficacy, as the initial procedure. Efficacy of stenting was weakly but significantly influenced by age at stenting and MLD before redilation.

Adverse events occurred in 23% of patients, and in 28% of procedures; however, severe events requiring surgery comprised only 3%. No patients in this survey died because of the procedure. Considering critical situations in which stenting is the primary option with no alternative method of dilating the stenosis, or it is a secondary option following previously ineffective treatment, the safety of stenting in this survey appears to be satisfactory.

The original Palmaz stent, which in Japan is still the most common stent for great vessel lesions, has disappeared from

clinical practice in most countries, and the efficacy in CHDs of innovative stents, such as the Palmaz Genesis and the Cheatham-Platinum stent, has been evaluated outside Japan.^{20–22} Furthermore, for coarctation, covered stent implantation is becoming a common procedure.^{23–25} In the present survey, we clarified that, even in Japan, the Genesis stent is gradually being introduced to real-life clinical practice. However, it is clearly off-label use and because of the limited specifications available in Japan, it has been used in strictly limited situations. We could not determine whether efficacy and safety differed between the original Palmaz and the Genesis stents. From this survey, there were no data to suggest that the type of stent may contribute to the acute outcome of stenting. As there was only 1 adverse event, which was a procedure-related stent fracture, during Genesis stent implantation, it may be safer to implant than the original Palmaz.

This survey collected data from 14 facilities, each of which performed more than 10 cases of stenting for stenosis of great vessels associated with CHDs. There were no standard guidelines among the responding facilities on indications for stenting, implanting procedure, follow-up plan, and indications for redilation. Furthermore, the retrospective nature of this study clearly limits the significance of the data. However, we believe the data will promote understanding of the current situation of stenting for stenosis of great vessels associated with CHDs in Japan. Although stenting for pulmonary vein stenosis had been reported,²⁶ it was excluded from this survey because the effectiveness of this procedure remains to be established.

As shown in this survey, stenting for CHDs is currently not only acceptably safe and effective, but also an indispensable treatment strategy in Japan. It is not ideal to leave such a strategy as an off-label use. We, the pediatric cardiology community, strongly recommend approving this procedure as officially covered by the health insurance system.

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In Vivo Dilatation of the Ductus Arteriosus Induced by Furosemide in the Rat

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ABSTRACT: Furosemide increases prostaglandin production and may be associated with patent ductus arteriosus (PDA). We aimed to clarify the *in vivo* ductus-dilating effects of furosemide in neonatal rats. Near-term rat pups delivered by a cesarean section were housed at 33°C. After a rapid whole-body freezing, the DA diameter was measured using a microscope and a micrometer. Pregnant rats (gestational day 21) were s.c. injected with furosemide 4 h before delivery, and the neonatal DA was examined 0, 15, 30, 60, and 120 min after birth. Furosemide was also s.c. injected into 60-min-old rats and the DA diameter was examined 30, 60, and 120 min later. The control rats showed a rapid postnatal DA constriction (diameter: 0.80 and 0.08 mm at 0 and 60 min after birth, respectively). Prenatally administered furosemide delayed postnatal DA closure (0.36 mm at 60 min after birth). Furosemide injection in 60-min-old rats dilated the constricted DA at 60 min (0.25 versus 0.02 mm in the controls). Indomethacin inhibited furosemide-induced DA dilatation. Furosemide delays DA closure and dilates the constricted DA in neonatal rats. If furosemide has similar effects in human preterm neonates, caution may be warranted in its use in the treatment of infants with PDA. (*Pediatr Res* 67: 173–176, 2010)

Furosemide is used to potentiate the natural diuresis seen in the preterm neonate to attenuate the severity of RDS in premature infants in the immediate postnatal period (1). It is also used to treat preterm infants with symptoms of renal toxicity induced by indomethacin, which is used to ameliorate a symptomatic patent ductus arteriosus (PDA) while preparing for pharmacological closure by indomethacin (2,3). Further, furosemide stimulates the renal production of prostaglandin E₂, a potent ductal smooth-muscle dilator (4–8). A previous retrospective study has provided evidence that treatment with the diuretic furosemide may increase the incidence of preterm PDA (9). In addition, a randomized controlled trial wherein furosemide and chlorothiazide were compared has revealed that furosemide increases the incidence of PDA in premature infants with RDS, presumably through a prostaglandin-mediated mechanism (10). Furosemide treatment may help in preventing heart failure due to PDA or indomethacin-induced toxicity but may also affect the ductal response to indomethacin. In a recent systematic literature review, it was found that furosemide treatment does not significantly increase

the risk of failure of ductal closure; however, the sample size of the review was insufficient in the above-mentioned risk (11).

The effects of furosemide on DA remain to be elucidated. We hypothesized that furosemide may increase prostaglandin E (PGE) secretion and dilate the DA of neonates *in vivo*. There is a transplacental effect of furosemide (12). The objective of this study was to elucidate the effect of furosemide on the patency of the ductus arteriosus in neonatal rats.

METHODS

Furosemide (Lasix) was purchased from Sanofi-Aventis Co. (Tokyo, Japan). Water-soluble indomethacin that could be used for injection was purchased from Banyu Pharmaceutical Co. (Tokyo, Japan).

The treatment protocol conformed to the guidelines issued by the American Physiologic Society, and our Institutional Ethical Committee for Animal Experiments approved the experimental protocol. Virgin Wistar rats were mated overnight from 1700 to 0900 h; the day on which sperm were detected in vaginal smears was regarded as gestational d 0 (total pregnancy period, 21.5 d). The rats were housed in a room under controlled environmental conditions, acclimatized to a 12-h light/12-h dark cycle, and maintained on commercial solid food and tap water available *ad libitum*. Experiments were performed on newborn rats delivered on gestational d 21.

Maternal administration. For studying the effect of furosemide in delaying postnatal DA closure, near-term pregnant rats (gestational day 21) were s.c. injected with furosemide (1, 10, and 100 mg/kg). The pregnant rats were subjected to atlas dislocation, and the pups were delivered by a cesarean section 4 h later. The newborn rats were incubated in a room at 33°C. To examine the *in situ* morphology of the postnatal DA, we used a rapid whole-body freezing method as described previously (13,14). In brief, the newborn rats were frozen at 0, 15, 30, 60, or 120 min after birth in acetone that had been cooled to –80°C in dry ice. The frozen thorax was cut along the frontal plane by using a freezing microtome (Komatsu Solidate Co. Ltd., Tokyo, Japan), and the inner diameters of the ascending aorta, main pulmonary artery, and DA were measured by observation under a microscope (Nikon Binocular Stereoscopic Microscope; Nihon Kogaku Co., Tokyo, Japan), using a micrometer (Nikon Ocular Micrometer; Nihon Kogaku Co., Tokyo, Japan). The DA of the newborn rats was 800–1200 μm in length, tubular along the middle three quarters of its length, and horn shaped at the proximal and distal ends (15). We measured the DA at 100-μm intervals, in 8–12 planes. The short axis was measured in ellipsoid images, assuming that the DA was round *in situ* (15). The smallest diameter recorded was used as an indicator of constriction. The ductus diameter was measured at 0, 15, 30, 60, and 120 min after birth (6–12 newborn rats for each dose and time point). The control rats showed a rapid postnatal DA constriction (diameter: 0.80, 0.28, 0.12, 0.08, and 0.02 mm at 0, 15, 30, 60, and 120 min after birth, respectively).

Immediate neonatal administration. In addition, we examined the effect of furosemide in delaying postnatal DA closure by performing the following experiment.

Near-term pregnant rats (gestational d 21) were subjected to atlas dislocation, and the pups were delivered by a cesarean section. Newborn rats were s.c. injected with furosemide (1 and 10 mg/kg in 5 mL saline) within 3 min

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Abbreviations: PDA, patent ductus arteriosus; PGE, prostaglandin E

after birth. The newborn rats were incubated in a room at 33°C. Using a rapid whole-body freezing method, the newborn rats were frozen at 0, 15, 30, 60, or 120 min after birth in acetone that had been cooled to -80°C in dry ice. As well as the above-mentioned method, the DA diameter was measured at 15, 30, 60, and 120 min after birth (6-14 rats for each dose and each time point). The control rats showed a rapid postnatal DA constriction (diameter: 0.80, 0.28, 0.12, 0.08, and 0.02 mm at 0, 15, 30, 60, and 120 min after birth, respectively).

Administration to neonates after postnatal DA closure. Reopening of the DA was examined as follows. Near-term pregnant rats (gestational d 21) were subjected to atlas dislocation, and the pups were delivered by a cesarean section. The newborn rats were incubated in a room at 33°C. Newborn rats were s.c. injected with furosemide (1 mg/kg in 5 µL saline), either alone or along with indomethacin (10 mg/kg) at 60 min after birth. Using a rapid whole-body freezing method, the newborn rats were frozen at 0, 30, 60, or 120 min after the s.c. injection with furosemide in acetone that had been cooled to -80°C in dry ice. As well as the above-mentioned method, the DA was examined at 30, 60, and 120 min after the injection (6-11 rats for each time point). The control rats showed a postnatal DA constriction (diameter: 0.02 and 0.0 mm at 120 and 180 min after birth, respectively).

Photographs. To observe constriction of the DA, the vessel was photographed in the frontal view with the help of a binocular stereoscopic microscope (Wild M400 Photomicroscope, Wild Heerbrugg Ltd., Heerbrugg, Switzerland) and color film (Reale; Fuji Film Co., Tokyo, Japan).

Statistics. The results are expressed as the mean ± SEM. The statistical significance of the differences between the group means was determined using a modified two-way ANOVA and the Bonferroni's method (16). The difference was considered significant if the *p* value was <0.05.

RESULTS

Maternal administration. In the control neonates, a rapid DA constriction was noted after birth. DA closure was delayed in the rats that were prenatally exposed to furosemide. All three doses of transplacentally administered furosemide induced a similar and significant delay in postnatal DA closure, as shown in Figure 1. Moreover, the degree of delay induced by the two higher doses of furosemide did not significantly differ from that induced by the clinical dose of furosemide (1 mg/kg). The DA diameter, 15 min after birth, was 0.28 mm in control, and 0.68, 0.64, and 0.54 mm after administration of 100, 10, and 1 mg/kg of furosemide, respectively. The DA diameter, 30 min after birth, was 0.12 mm in control, and 0.30, 0.31, and 0.39 mm after administration of 100, 10, and 1 mg/kg of furosemide, respectively. The DA diameter, 60 min

after birth, was 0.08 mm in control, and 0.23, 0.27, and 0.23 mm after administration of 100, 10, and 1 mg/kg of furosemide, respectively. The DA diameter, 120 min after birth, was 0.02 mm in control, 0.01, and 0.05 mm after administration of 100 and 10 mg/kg of furosemide, respectively.

Immediate neonatal administration. Subcutaneous injection of furosemide (1 mg/kg) at birth significantly delayed DA closure, as shown in Figure 2. The higher dose (10 mg/kg) induced a significantly greater delay in DA closure than the lower dose (1 mg/kg; Fig. 3). The DA diameter, 15 min after birth, was 0.28 mm in control, 0.82 mm and 0.69 mm after administration of 10 mg/kg and 1 mg/kg of furosemide, respectively. The DA diameter, 30 min after birth, was 0.12 mm in control, and 0.48 mm and 0.36 mm after administration of 10 and 1 mg/kg of furosemide, respectively. The DA diameter, 60 min after birth, was 0.08 mm in control, and 0.28 mm and 0.18 mm after administration of 10 and 1 mg/kg of furosemide, respectively. The DA diameter, 120 min after birth, was 0.02 mm in control, and 0.14 mm and 0.02 mm after administration of 10 and 1 mg/kg of furosemide, respectively.

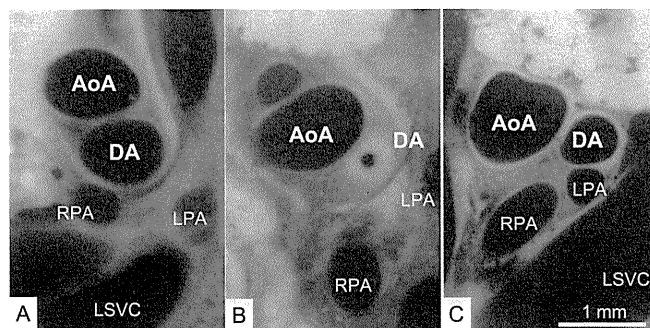


Figure 2. The neonatal thorax cut along the frontal plane, at the level of the DA. A, The dilated DA in a newborn rat (at 0 min after birth; control). B, The constricted, thick-walled DA in a 30-min-old rat (control). C, The semiconstricted DA in a 30-min-old newborn rat s.c. injected with furosemide (1 mg/kg) at birth. AoA, aortic arch; DA, ductus arteriosus; LPA, left pulmonary artery; L SVC, left superior vena cava; RPA, right pulmonary artery.

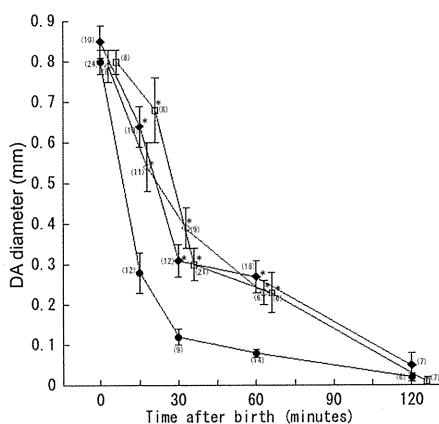


Figure 1. The time course of postnatal DA closure in the control rats (●) and in rats that were transplacentally exposed to furosemide (1 mg/kg ◇), 10 mg/kg (◆), or 100 mg/kg (□) injected s.c. at 4 h before birth. The x axis shows the time after birth in minutes. The y axis shows the DA diameter. Each point was obtained from the study of 6-24 neonates. Each value expressed as mean ± SEM. **p* < 0.05 vs the controls.

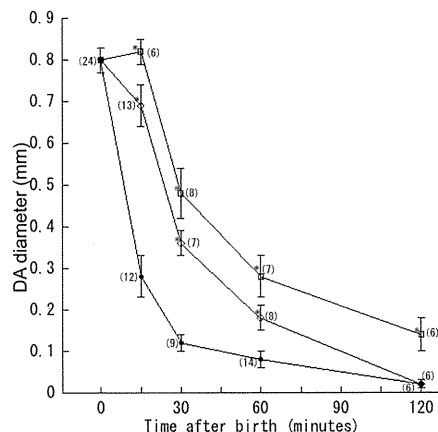


Figure 3. The time course of postnatal DA closure in the control rats (●) and in rats that were administered furosemide at a dose of 1 mg/kg (◇) or 10 mg/kg (□) at birth. The x axis shows the time after birth in minutes. The y axis shows the DA diameter. Each point was obtained from the study of 6-24 neonates. Each value expressed as the mean ± SEM. **p* < 0.05 vs the controls.

Administration to neonates after successful DA closure.

Figure 4 shows that s.c. injection of furosemide at 60 min after birth induced DA reopening to a moderate degree. Peak dilatation was observed at 60 min after the injection (Fig. 5). The DA diameter, 30 min after injection (90 min after birth), was 0.06 mm in control, and 0.14 mm after administration of furosemide (1 mg/kg) alone and 0.05 mm after administration of furosemide (1 mg/kg) with indomethacin (1 mg/kg), respectively. The DA diameter, 60 min after injection (120 min after birth), was 0.02 mm in control, and 0.25 mm after administration of furosemide (1 mg/kg) alone and 0.10 mm after administration of furosemide (1 mg/kg) with indomethacin (1 mg/kg), respectively. The DA diameter, 120 min after injection (180 min after birth), was 0.00 mm in control, and 0.04 mm after administration of furosemide (1 mg/kg) alone and 0.10 mm after administration of furosemide (1 mg/kg) with indomethacin (1 mg/kg), respectively. The furosemide-induced DA dilatation was considerably, but not completely, inhibited with the simultaneous administration of indomethacin (Fig. 5).

DISCUSSION

This is the first *in vivo* study to experimentally demonstrate that postnatal DA closure is delayed after furosemide exposure in rats.

A previous randomized controlled trial wherein furosemide and chlorothiazide were compared has revealed that furosemide increases the incidence of PDA in preterm infants with RDS (9), presumably through a prostaglandin-mediated mechanism (10). Green *et al.* (9,10,17,18) suggested that furosemide treatment might adversely affect the patency rate of the immature DA. Apart from these studies, there has been limited research on the effects of furosemide on preterm individuals with PDA (11). In a recent systematic literature review, it was found that furosemide treatment does not significantly increase the risk of failure of DA closure; however, the sample size of the review was insufficient to rule out even a 31% increase in the risk (11). We hypothesized that if furosemide stimulates the renal synthesis of PGE in preterm infants, it should be able to delay postnatal DA closure and inhibit the constrictive effect of indomethacin in infants. In this study, we found that postnatal furosemide treatment delays ductal closure and dilates the constricted DA in neonatal rats in a dose-dependent manner. However, the ductus-dilating effect of furosemide, even when administered at a high dose (10 mg/kg) is merely modest. Various clinical and experimental studies have demonstrated that furosemide alters systemic vascular resistance in a manner that is independent of its diuretic action. Most previous studies have implicated prostaglandins synthesized in the kidney (5,8,19,20) or DA wall (21) as mediators of this effect of furosemide. Friedman *et al.* studied the urinary excretion of PGE in seven sick, low birth weight infants. They found that the excretion rate increased (from 0.4 to 1.3 ng/mg Cr) in all the patients after furosemide treatment but decreased in two patients after indomethacin treatment (6). These results indicated that furosemide enhances the urinary excretion of PGE by mechanisms that may reflect increased prostaglandin synthesis, decreased prostaglandin metabolism in the kidneys, or both (6). Neonatal blood PGE concentrations were not studied in our study. In our study, the administration of furosemide at 60 min after birth dilated the constricted DA of the neonates and indomethacin attenuated the effects of furosemide because it still differs from the controls (Fig. 5). We speculate that prostaglandins synthesized in the kidney, in response to furosemide treatment, may mediate the effects of furosemide on the DA.

In our study, on pregnant rats and their neonates, we found that when administered at the usual clinical dose (0.5–1.0 mg/kg) for the mother and the newborn infant, furosemide has a significant effect in delaying postnatal DA closure and reopening the constricted DA. In fetuses with indomethacin-induced DA constriction, PDE-3 and PDE-5 inhibitors dilate the DA more sensitively in preterm rats than in near-term rats (22,23). Clyman (24) has demonstrated that compared with the DA in near-term lambs, the DA in immature lambs is considerably more sensitive to the dilating effects of PGE. Therefore, we speculate that a) the DA in preterm animals is more sensitive to furosemide than that in full-term animals

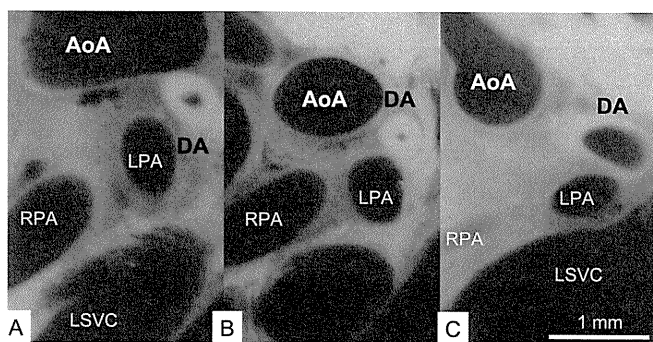


Figure 4. The neonatal thorax cut along the frontal plane, at the level of the ductus arteriosus (DA). A, The constricted DA in a 60-min-old rat (control). B, The constricted, thick-walled DA in a 120-min-old rat (control). C, The dilated DA in a 120-min-old rat that was s.c. injected with furosemide (1 mg/kg) 60 min after birth. AoA, aortic arch; DA, ductus arteriosus; LPA, left pulmonary artery; LSVC, left superior vena cava; RPA, right pulmonary artery.

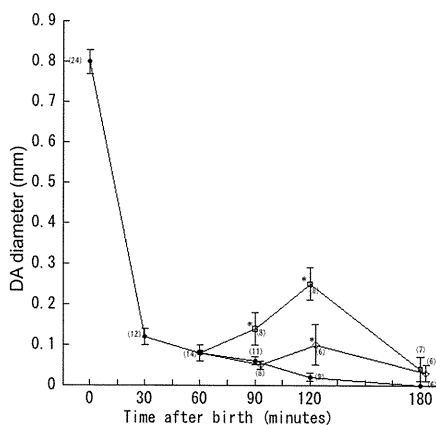


Figure 5. The time course of postnatal DA closure in the control rats (●) and in rats that were administered 1 mg/kg furosemide alone (□) or in combination with 10 mg/kg indomethacin (◇) at 60 min after birth. The x axis shows the time after birth in minutes. The y axis shows the DA diameter. Each point was obtained from the study of 6–24 neonates. Each value expressed as the mean ± SEM. **p* < 0.05 vs the controls.

and (b) in clinical settings too, furosemide exposure may result in delayed postnatal DA closure and attenuate the constrictive effect of indomethacin in premature infants. We recommend that furosemide be used with caution in the treatment of preterm infants with symptomatic PDA and heart or renal failure. However, the other beneficial effects of furosemide, for example, its diuretic effects, may balance its harmful effects in patients with PDA. In our study, the duration in ductus-dilating effect of furosemide is at least short in the newborn rats. Therefore, clinical observations on the effect of furosemide on the DA are warranted.

In conclusion, furosemide attenuates postnatal DA constriction in neonatal rats. If the ductus arteriosus is affected in a similar manner in human preterm neonates and this is an assumption, caution may be warranted in the use of furosemide in the treatment of preterm infants with PDA.

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Guidelines for Diagnosis and Management of Cardiovascular Sequelae in Kawasaki Disease (JCS 2008)

– Digest Version –

JCS Joint Working Group

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Introduction of the Revised Guidelines

More than forty years have passed since 1967, when the first case series of Kawasaki disease was reported.¹ Currently, more than half of the patients diagnosed with Kawasaki disease are 16 years of age or older. In Japan, Kawasaki disease is now managed not only by pediatricians but also by internists. As this timeline suggests, it is expected that more than half of the patients with cardiovascular sequelae of Kawasaki disease have reached adulthood. However, since Kawasaki disease develops most frequently by around 1 year of age, many internists are still not familiar with it (Table 1). The main cardiovascular disease caused by Kawasaki disease is vasculitis, and in this respect patients with this disease differ significantly from other adult patients with arteriosclerosis and/or hypertension. Since the number of adult patients with a history of Kawasaki disease will increase over time, pediatric cardiologists need to accurately provide their findings on Kawasaki disease to cardiovascular internists. Reliable means are needed to ensure appropriate diagnosis, treatment, and

determination of the prognosis of patients with cardiovascular sequelae in Kawasaki disease. We hope the present guidelines will help healthcare professionals diagnose and treat their patients with Kawasaki disease.

No major additions or corrections of the revised guidelines presented here have been made. The present guidelines basically follow the previous version of the guidelines. However, since the number of adult patients with coronary artery lesions and a history of Kawasaki disease is growing increasingly larger over time, in the present guidelines additional descriptions are included of the risk of development of arteriosclerosis, mechanism of development of arteriosclerosis, and prevention and treatment of arteriosclerosis in patients with a history of Kawasaki disease, particularly those with coronary artery lesions. The recent advancement of diagnostic imaging techniques has been impressive, and there are many techniques useful in the diagnosis and treatment of coronary artery lesions due to Kawasaki disease. The present

Table 1. Diagnostic Guidelines of Kawasaki Disease (MCLS: Infantile Acute Febrile Mucocutaneous Lymph Node Syndrome)

This is a disease of unknown etiology affecting most frequently infants and young children under 5 years of age. The symptoms can be classified into two categories, principal symptoms and other significant symptoms or findings.

A. Principal symptoms

1. Fever persisting 5 days or more (inclusive of those cases in whom the fever has subsided before the 5th day in response to therapy)
2. Bilateral conjunctival congestion
3. Changes of lips and oral cavity: Redding of lips, strawberry tongue, diffuse injection of oral and pharyngeal mucosa
4. Polymorphous exanthema
5. Changes of peripheral extremities:
(Acute phase): Redding of palms and soles, Indurative edema
(Convalescent phase): Membranous desquamation from fingertips
6. Acute nonpurulent cervical lymphadenopathy

At least five items of 1 to 6 should be satisfied for diagnosis of Kawasaki disease.

However, patients with four items of the principal symptoms can be diagnosed as Kawasaki disease when coronary aneurysm or dilatation is recognized by two-dimensional (2D) echocardiography or coronary angiography.

B. Other significant symptoms or findings

The following symptoms and findings should be considered in the clinical evaluation of suspected patients.

1. Cardiovascular: Auscultation (heart murmur, gallop rhythm, distant heart sounds), ECG changes (prolonged PR/QT intervals, abnormal Q wave, low-voltage QRS complexes, ST-T changes, arrhythmias), chest X-ray findings (cardiomegaly), 2D echo findings (pericardial effusion, coronary aneurysms), aneurysm of peripheral arteries other than coronary (axillary, etc.), angina pectoris or myocardial infarction
2. Gastrointestinal (GI) tract: Diarrhea, vomiting, abdominal pain, hydrops of gallbladder, paralytic ileus, mild jaundice, slight increase of serum transaminase
3. Blood: Leukocytosis with shift to the left, thrombocytosis, increased erythrocyte sedimentation rate (ESR), positive C-reactive protein (CRP), hypoalbuminemia, increased α 2-globulin, slight decrease in erythrocyte and hemoglobin levels
4. Urine: Proteinuria, increase of leukocytes in urine sediment
5. Skin: Redness and crust at the site of BCG inoculation, small pustules, transverse furrows of the finger nails
6. Respiratory: Cough, rhinorrhea, abnormal shadow on chest X-ray
7. Joint: Pain, swelling
8. Neurological: Cerebrospinal fluid (CSF) pleocytosis, convulsion, unconsciousness, facial palsy, paralysis of the extremities

Remarks

1. For item 5 under principal symptoms, the convalescent phase is considered important.
2. Nonpurulent cervical lymphadenopathy is less frequently encountered (approximately 65%) than other principal symptoms during the acute phase.
3. Male: Female ratio: 1.3 to 1.5:1, patients under 5 years of age: 80 to 85%, fatality rate: 0.1%
4. Recurrence rate: 2 to 3%, proportion of siblings cases: 1 to 2%
5. Approximately 10% of the total cases do not fulfill five of the six principal symptoms, in which other diseases can be excluded and Kawasaki disease is suspected. In some of these patients coronary aneurysms (including so-called coronary artery ectasia) have been confirmed.

Prepared by the Kawasaki Disease Research Group of the Ministry of Health, Labor, and Welfare, 5th revised edition.

Table 2. Classification of Severity of Cardiovascular Lesions in Kawasaki Disease

(a) Classification of coronary aneurysms during the acute phase

Small aneurysms (ANs) or dilatation (Dil): localized dilatation with ≤ 4 mm internal diameter

In children ≥ 5 years of age, the internal diameter of a segment measures < 1.5 times that of an adjacent segment

Medium aneurysms (ANm): aneurysms with an internal diameter from > 4 mm to ≤ 8 mm

In children ≥ 5 years of age, the internal diameter of a segment measures 1.5 to 4 times that of an adjacent segment

Giant aneurysms (ANI): aneurysms with an internal diameter of > 8 mm

In children ≥ 5 years of age, the internal diameter of a segment measures > 4 times that of an adjacent segment

(b) Severity classification

The severity of Kawasaki disease is classified into the following 5 grades on the basis of findings of echocardiography and selective coronary angiography or other methods:

- I. No coronary dilatation: patients with no coronary dilatation including those in the acute phase
- II. Transient coronary dilatation during the acute phase: patients with slight and transient coronary dilatation which typically subsides within 30 days after onset
- III. Regression: patients who still exhibit coronary aneurysms meeting the criteria for dilatation or more severe change on day 30 after onset, despite complete disappearance of changes in the bilateral coronary artery systems during the first year after onset, and who do not meet the criteria for Group V
- IV. Remaining coronary aneurysm: patients in whom unilateral or bilateral coronary aneurysms are detected by coronary angiography in the second year or later and who do not meet the criteria for Group V
- V. Coronary stenotic lesions: patients with coronary stenotic lesions detected by coronary angiography
 - (a) Patients without ischemic findings: patients without ischemic signs/symptoms detectable by laboratory tests or other examinations
 - (b) Patients with ischemic findings: patients with ischemic signs/symptoms detectable by laboratory tests or other examinations

Other clinical symptoms of findings: When patients have moderate or severe valvular disease, heart failure, severe arrhythmia, or other cardiac disease, such conditions should be described in addition to the severity of Kawasaki disease.

guidelines thus describe in detail current knowledge on diagnostic imaging techniques used to evaluate coronary artery lesions. We also discuss the genetic background of Kawasaki disease, although findings regarding this still limited.

We previously discussed the classification of coronary artery lesions during the acute phase of Kawasaki disease. Although the criteria for small aneurysms and giant aneurysms were slightly questioned, we decided that no modifications of the criteria needed to be made, based on the opinions of members and collaborators such as that no new evidence have been provided on this matter, and that the classification may not be revised in the present guidelines because it will not affect the contents of the present guidelines for the diagnosis and treatment of cardiovascular sequelae in Kawasaki disease. We used the conventional classification to prepare the present guidelines (Table 2).

Although the present guidelines are based in principle on available evidence, the diagnosis and treatment of sequelae in Kawasaki disease are often based on case reports.

Table 3. Levels of Recommendations

Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective.
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion regarding the usefulness/efficacy of a procedure or treatment.
Class III	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and may in some cases be harmful.

Emphasis was therefore placed on case reports in the present guidelines as well. Table 3 lists the criteria for levels of recommendations on the procedure and treatment of cardiovascular sequelae in Kawasaki disease.

I Current Epidemiology of Kawasaki Disease, and Advancement in and Topics Related to Acute Phase Treatment

1. Current Epidemiology of Kawasaki Disease

According to the 19th national survey on Kawasaki disease (2005 to 2006),² the number of patients diagnosed was 10,041 in 2005 and 10,434 in 2006, yielding a total of 20,475 patients. The mean prevalence during the 2-year survey period was 184.6 patients/100,000 children 0 to 4 years of age (male 209.3, female 158.6). The total number of patients with Kawasaki disease including those patients reported in the 19th national survey is 225,682 (male 130,827, female 94,855) as

of December 31, 2006. About 90,000 patients were ≥ 20 years of age as of January 2006.³

2. Mortality and Prognosis of Patients With Kawasaki Disease

The mortality of patients with Kawasaki disease has gradually decreased, from 0.13% in 1989 to 0.01% in the latest survey.

In a cohort study of 6,576 patients followed for about 20

years,⁴ the standardized mortality ratio (SMR) was 1.14 overall and 0.71 in patients after the acute phase. The mortality rate in male patients with cardiac sequelae in Kawasaki disease was 2.55, and significantly higher than the overall rate.

3. Advancement in Intravenous Immunoglobulin (IVIG) Therapy

During the acute phase, about 86% of patients received IVIG therapy in the 19th national survey.² Among patients undergoing initial IVIG therapy, 16.2% received an additional IVIG therapy after the initial therapy, and 4.5% of patients received steroids (including patients receiving additional IVIG therapy and those receiving a combination of IVIG and steroids). Pulse steroid therapy was performed in 3.0% of patients and non-pulse steroid therapy in 2.5% (including patients undergoing both pulse therapy and non-pulse therapy).

4. Changes Over Time in the Incidence of Coronary Artery Lesion

The prevalence of coronary artery lesion during the acute phase has decreased over time: 18.1% in 1997 to 2000 (coronary dilatation 14.7%, aneurysm 2.9%, giant aneurysm 0.50%), 14.8% in 2001 to 2004 (coronary dilatation 11.6%, aneurysm 1.9%, giant aneurysm 0.36%),⁵ and 11.9% in the 19th survey (coronary dilatation 10.1%, aneurysm 1.5%, giant aneurysm 0.35%).²

The prevalence of coronary artery lesion observed as sequelae in Kawasaki disease has also decreased, from 6.2% in 1997 to 2000 (coronary dilatation 3.9%, aneurysm 1.9%, giant aneurysm 0.46%), to 4.5% in 2001 to 2004 (coronary

dilatation 2.8%, aneurysm 1.3%, giant aneurysm 0.33%), and 3.7% in the 19th survey (coronary dilatation 2.3%, aneurysm 1.0%, giant aneurysm 0.35%). The improvement of clinical results may be explained by the increase in frequency of use of single-dose treatment with immunoglobulin 2g/kg from 8% to 68%.

5. Advancement in Treatment for Patients Not Responding to IVIG Therapy

It is important to treat patients not responding to initial IVIG therapy, who account for about 15% of children with Kawasaki disease, and additional treatments with IVIG, steroid, ulinastatin, and plasmapheresis has been performed for them. Although immunosuppressive agents, such as cyclosporine and infliximab are also used currently, the efficacy and safety of these drugs in the treatment of Kawasaki disease have yet to be established.

6. Problems With Incomplete (Atypical) Kawasaki Disease

The incidence of coronary artery lesions in patients exhibiting 4 principal symptoms of Kawasaki disease is slightly higher than that in patients with 5 to 6 principal symptoms.⁶ Presentation of a small number of principal symptoms does not necessarily indicate mild disease. Patients with at least 4 principal symptoms require treatment identical to that for patients with complete (typical) Kawasaki disease, and patients with ≤ 3 principal symptoms should be treated similarly to those with complete Kawasaki disease.

II Pathology, Pathophysiology, and Natural History of Cardiac Sequelae in Kawasaki Disease

1. Coronary Artery Lesions

The incidence of coronary aneurysm as a sequelae of Kawasaki disease was 16.7% in 1983, when aspirin was the main component of acute phase treatment, but decreased to 3.8% in 2007 as the use of high-dose gamma globulin therapy increased.² The mortality rate of children with Kawasaki disease was above 1% by 1974, but decreased to around 0.1% in 1990s and is currently 0.01%.²

1 Development of Coronary Aneurysms

Coronary artery lesions are observed during the initial acute phase of Kawasaki disease by echocardiography in all patients as increased echo intensity of the coronary artery wall an average of 5.4 days after onset.⁷ Coronary dilatation subsides during the initial acute phase, ie, within 30 days after onset, and is referred to as transient coronary dilatation,⁷ while coronary aneurysms persisting during the convalescence phase or later are considered sequelae of Kawasaki disease. The incidences of coronary sequelae have decreased to 10.09%, 1.49%, and 0.35% in the case of coronary dilatation, aneurysms, and giant aneurysms, respectively.² It is important to examine for persistent aneurysms using echocardiography

during the early stage and about 30 days after the onset of Kawasaki disease.

2 Prognosis (Table 2 and Table 4)

(1) Reduction and Regression of Aneurysms

Coronary aneurysms remaining ≥ 30 days after the onset of Kawasaki disease typically decrease in size during the convalescence phase or later. "Regression" of coronary aneurysms, ie, disappearance of abnormal findings on coronary angiography (CAG), often occurs within 1 to 2 years after onset and typically occurs in the case of small or medium aneurysms.⁸ This regression has been reported to occur in 32⁹ to 50%¹⁰ of patients. It has been reported that patients may develop stenosis of vessels¹¹ that have exhibited regression, decrease in coronary diastolic function,¹² abnormal vascular endothelial function, and substantial intimal hyperplasia,¹³⁻¹⁴ which have been suggested to lead to juvenile arteriosclerosis. Patients should thus be followed up even after regression of coronary aneurysms.¹⁵

(2) Occlusion of Aneurysms

Medium and giant aneurysms are often associated with thrombotic occlusion in the relatively early stage of Kawasaki

Table 4. Classification of Coronary Artery Lesions by Angiographic Findings

- Dilatation lesions: DL (ANI, ANm, ANs, or Dil, as defined in echocardiography-based classification [Table 2])
- Stenotic lesions: SL
- Occlusion: OC, 100% SL
- Segmental stenosis: SS [recanalized vessel] (See Figure 1)
 - A. Braid-like lesion: multiple regions of neovascularizations within the thrombotic occlusion
 - B. Bridging lesion: development of nutrient arteries distal to an occluded aneurysm
 - C. Pericoronary artery communication: anterograde blood flow with a communication of two points in one coronary artery via an existing vessel
- Local stenosis: LS

Subcommittee on Standardization of Coronary Artery Lesions due to Kawasaki Disease, "the Kawasaki Disease Research Group", Ministry of Health and Welfare, 1983.

disease. While coronary occlusions are associated with myocardial infarction and sudden death, approximately two-thirds patients with them are asymptomatic.¹⁶ It is typical of Kawasaki disease that coronary occlusion is followed by the development of recanalized vessels and collateral flows which significantly improve findings of myocardial ischemia.¹⁷ However, patients may often suffer symptoms of myocardial ischemia during adolescence, and may require bypass surgery or develop heart failure and arrhythmias.

(3) Recanalization (Segmental Stenosis)

Neovascularization considered to represent recanalization after occlusion is referred to as segmental stenosis. Segmental stenosis is observed in 15% of patients with coronary artery lesions due to Kawasaki disease, and occurs in the right coronary artery in 90% of such patients¹⁶; occlusion and recanalization in the right coronary artery are considered more common. Angiographic findings of segmental stenosis are classified into three types according to their pathophysiology, time of onset, and prognosis¹⁷ (Figure 1).

(4) Localized Stenosis

During the period up to 10 to 21 years after onset, localized stenoses of $\geq 75\%$ vessel diameter develop in 4.7 to 12% of patients with coronary artery lesions, and often occur in the proximal segment or the main trunk of the left anterior descending artery.¹⁸ Although progression to stenosis is more common in the case of giant aneurysms, it has been suggested that even small aneurysms with a diameter of 5 to 6 mm on angiography may progress to stenosis during long-term follow-up.⁹ Evaluation with intravascular ultrasound (IVUS) has revealed intimal hyperplasia in aneurysms with an internal diameter of >4 mm, which may progress to stenosis.¹⁹

(5) Coronary Arteries Without Aneurysm Formation

Slight or moderate intimal hyperplasia in coronary arteries without aneurysm formation has been reported in patients with Kawasaki disease,^{12,14} and whether a history of Kawasaki disease is a risk factor for development of atherosclerotic lesions has been discussed.

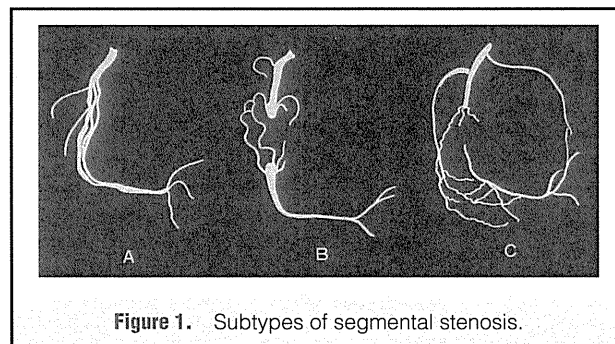


Figure 1. Subtypes of segmental stenosis.

Table 5. Characteristics of Myocarditis During the Acute Phase of Kawasaki Disease

Myocarditis during the acute phase of Kawasaki disease

- is often transient
- is often associated with a slight decrease in left ventricular ejection fraction
- is often associated with transient pericardial effusion
- is associated with transient abnormalities of all valves, among which slight mitral insufficiency and aortic insufficiency may persist
- is rarely associated with severe myocarditis.

2. Myocardial Injury

Myocardial injury is classified mainly into two types: inflammatory myocardial injury associated with myocarditis or valvulitis during the acute phase, and ischemic myocardial injury secondary to coronary aneurysms or microcirculation disorder due to coronary arteritis.

1 Inflammatory Lesions

Interstitial myocarditis and pericarditis are major inflammatory heart diseases associated with Kawasaki disease. The presence of myocarditis during the acute phase has been detected with gallium (Ga)-67 myocardial scintigraphy.²⁰ Cell infiltration mainly by monocytes is a main pathological finding, while degeneration and necrosis of myocytes are rare. Table 5 lists the characteristics of myocarditis in Kawasaki disease.

2 Ischemic Lesions

Acute myocardial infarction (AMI) due to stenotic lesions adjacent to coronary aneurysms caused by severe coronary arteritis tends to develop during the second week after onset or later. Progression of coronary aneurysms to stenotic lesions is more prevalent in aneurysms with an internal diameter of ≥ 6 mm, and is especially prevalent in giant aneurysms with a diameter of ≥ 8 mm. Chronic myocardial infarction is observed more often after the first 7 weeks of disease, following the acute phase.

3 Lesions in the Conducting System

During the acute phase, inflammation of the conducting system is observed, and transient atrioventricular block, premature ventricular contraction, supraventricular tachycardia, or ventricular tachycardia may develop as clinical manifestations of injury to the conducting system.

3. Valvular Disease

Slight and transient mitral, tricuspid, or pulmonary valve insufficiency is often observed by Doppler echocardiography during the acute phase of Kawasaki disease, and aortic valve insufficiency is also observed in rare cases.²¹ In addition to regurgitation due to myocarditis and valvulitis during the acute phase, regurgitation may also develop during the remote phase due to thickness or deformation of valves with fibrosis after valvulitis, or to papillary muscle dysfunction caused by ischemia²²⁻²⁴ (Figure 2). The incidence of valvular disease is reported to be 1.88% during the acute phase and 0.41% or later.²

4. Arteriosclerosis (Especially Progression to Atherosclerosis)

The progression of vessel disorders due to Kawasaki disease, and especially that of coronary artery lesions to sclerotic lesions, has been described in detail.^{14,25-29} Recent clinical studies have revealed that abnormal diastolic function of peripheral vessels and changes in endothelial cell biomarkers of vascular endothelial dysfunction are present during the remote phase regardless of the presence or absence of coronary artery lesions.³⁰⁻³² However, there is no clinical evidence clearly indicating whether the incidence of atherosclerosis, a finding of lifestyle-related diseases commonly observed in adults, is higher in individuals with a history of Kawasaki disease. Long-term, large-scale, continuous clinical studies will be needed to answer this question.

Careful and detailed investigations of the development and progression of arteriosclerotic lesions after Kawasaki disease are needed to clarify the mechanisms underlying them and determine how to prevent the development/progression of such lesions, in ensuring appropriate long-term management of patients.

5. Non-Coronary Vessel Disorders

Aneurysms of the axillary arteries, femoral arteries, iliac arteries, renal arteries, abdominal aorta, and internal mammary arteries have been observed in rare cases (0.6³³ to 2%³⁴), and all patients with peripheral aneurysms in these arteries have large coronary aneurysms. Cases of necrotic lesions of the fingers, cerebral infarction due to cerebrovascular disorders, renovascular hypertension, shock due to rupture of femoral arteries, replacement of large abdominal aneurysms with vascular prostheses, and coating of aneurysms have been reported in patients with a history of Kawasaki disease. Although in many cases aneurysms in the axillary arteries and other vessels regress within 1 to 2 years, a case of abrupt occlusion after 35 years has been reported.³⁵ Patients with aneurysms of the peripheral arteries should thus be followed for a long period of time.

6. Summary of Pathology, Pathophysiology, and Natural History of Cardiac Sequelae

1 Coronary Artery Lesions

Although significant infiltration of inflammatory cells in the coronary arteries during the acute phase of Kawasaki disease regresses over time, a large number of inflammatory cells may remain in the intima, and endarteritis may persist for a long period of time even after remission of clinical symptoms.^{36,37} During the remote phase, vascular smooth muscle cells continue to multiply actively at the inlet and outlet of the aneurysm,²⁹ and concentric intimal hyperplasia may induce stenosis or occlusion. When an aneurysm becomes clogged by a clot, a new artery with multiple lumens is often formed through the clot. The prognosis in such cases of myocardial ischemia is thus often fair.¹⁷ However, such spontaneous recanalization develops only when sudden death or severe myocardial infarction does not occur at the time of occlusion. Patients with medium or giant aneurysms and those with progressive localized stenosis are continuously at risk of sudden death and/or myocardial infarction. It is therefore believed

