Assessment of Platelet Thrombus Formation under Flow Conditions in Patients with Acute Kawasaki Disease

Nobuyuki Tsujii, MD, PhD[1], Keiji Nogami, MD, PhD[1], Hiroyuki Yoshizawa, MD, PhD[1], Toshiyuki Sakai, MD, PhD[2], Kazuyoshi Fukuda, MD, PhD[3], Akira Ishiguro, MD, PhD[4], and Midori Shima, MD, PhD[1]

Objective To assess platelet thrombus formation (PTF) under flow conditions in patients with Kawasaki disease. Previously available platelet activation data were limited for nonphysiological shear stress condition. The total thrombus-formation analysis system (T-TAS) was developed for quantitative PTF analysis.

Study design In total, 33 patients with acute Kawasaki disease were assessed. Whole blood samples, obtained immediately before treatment and 1 week and 1 month after treatment, were assessed using the T-TAS with a collagen-coated platelet chip under high shear values (1000 s^{-1} [PL_{12}] and 2000 s^{-1} [PL_{24}]). Measures, such as time to reach 5 kPa above the base pressure ($T_{5+\alpha}$) and area under the curve for flow pressure curve for 10 minutes (AUC_{10}) were analyzed to quantify PTF.

Results Immediately before treatment, the median PL_{12}-$T_{5+\alpha}$ and PL_{24}-$T_{5+\alpha}$ were 3.3 minutes (IQR 2.0-4.5) and 1.3 minutes (0.9-1.9), respectively, and both values were significantly lower in adult controls (3.5 minutes [2.9-6.4] and 2.8 minutes [1.8-4.8]; $P = .015$ and $P < .001$, respectively). In addition, the PL_{12}-AUC_{10} (151.7 U [94.5-279.9]) significantly decreased in adult controls (234.1 U [110.5-306.5], $P = .007$). By contrast, at 1 week and 1 month after the start of treatment, the $T_{5+\alpha}$ was longer, and the PL_{12}-AUC_{10} and PL_{24}-AUC_{10} decreased.

Conclusions In patients with acute Kawasaki disease, the PTF had an early onset and weak stability. *(J Pediatr 2020;226:266-73)*.

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Kawasaki disease is an acute systemic vasculitis, of unknown etiology, that is mainly observed in infants and young children.[1] Individuals with Kawasaki disease can suffer damage to the vascular endothelial cells in small- and medium-sized arteries, most commonly in the coronary arteries. This may lead to coronary thrombosis, myocardial infarction, and life-threatening aneurysms.[2] The acute phase of Kawasaki disease involves platelet activation,[3] and antiplatelet therapy with aspirin was included in the treatment protocol in the past decades. However, previously available platelet activation data were limited for nonshear stress condition and not available for shear stress condition.[4] A newly automated microchip flow chamber system (total thrombus-formation analysis system [T-TAS]) has been developed for the quantitative analysis of platelet thrombus formation (PTF) using microchips with thrombogenic surfaces.[5] In the current study, we assessed PTF under different flow conditions to validate platelet activation characteristics and the effect of antiplatelet therapy in patients with acute Kawasaki disease.

Methods

The medical research ethics committees of the participating institutions approved this study. Pediatric patients with Kawasaki disease were investigated after written informed consent was obtained from the parents. The patients were admitted to Nara Medical University Hospital, Kokuho Central Hospital, and Saiseikai Chuwa Hospital in Japan between January 2011 and June 2017.

AUC_{10}	Area under the curve for flow pressure curve for 10 minutes
CAL	Coronary artery lesion
GP	Glycoprotein
IVIG	Intravenous immunoglobulin
PL_{12}	Platelet chips at flow rates of 12 μL min^{-1}
PL_{24}	Platelet chips at flow rates of 24 μL min^{-1}, Pre Immediately before treatment
PTF	Platelet thrombus formation
T-TAS	Total thrombus-formation analysis system

From the [1]Department of Pediatrics, Nara Medical University, Kashihara; [2]Department of Pediatrics, Kokuho Central Hospital, Shiki; [3]Department of Pediatrics, Saiseikai Chuwa Hospital, Sakurai, Nara, Japan; and [4]Department of Postgraduate Education and Training, National Center for Child Health and Development, Tokyo, Japan

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They were diagnosed with Kawasaki disease according to the criteria published by the Japanese Circulation Society.[6] Therapeutic management during the acute phase of Kawasaki disease was standardized in accordance with these guidelines. All patients received antiplatelet agents and intravenous immunoglobulin (IVIG) treatment as first-line therapy. IVIG was administered as a single infusion of 2 g/kg or 2 infusions of 1 g/kg daily. Meanwhile, aspirin was administered as an antiplatelet agent at a dose of 30-50 mg/kg/day during the acute phase and, subsequently, at 3-5 mg/kg/day during convalescence. In patients with elevated liver enzyme levels, or during an influenza epidemic, flurbiprofen was administered at a dose of 3-5 mg/kg/day. The patients who received intravenous injection of acetaminophen, which suppresses platelet activation, were excluded.[7] Nonresponders are defined as individuals requiring additional treatment for fever lasting more than 24 hours after the end of IVIG infusion or recrudescent fever associated with Kawasaki disease symptoms after an afebrile period.[6] Based on a previous study, coronary artery lesions (CALs), including aneurysms, are defined using the Japanese diagnostic guidelines.[6] Cardiovascular specialists assessed coronary artery anomalies via 2-dimensional echocardiography. Abnormal coronary arteries were defined as arteries with a luminal diameter >3.0 mm in a child age younger than 5 years and >4.0 mm in those age 5 years and older. Cardiovascular lesions were graded if an arterial segment's internal diameter was at least 1.5-fold larger than that of the adjacent segment or if the lumen was irregular.

Whole blood samples were obtained via venipuncture and placed in hirudin-anticoagulant tubes at 3 time-points: immediately before treatment (Pre) and 1 week and 1 month after the start of treatment. The blood samples were kept at room temperature for at least 1 hour after collection, and then the tests were performed. Blood samples obtained from 19 healthy individuals age 20-40 years were prepared for adult control, from 11 healthy individuals age 1-146 (median; 26) months for child control, and from 5 febrile children age 7-116 (median; 26) months for febrile control, which was used as the standard reference.

To analyze flow-based thrombus formation, the modified T-TAS (Fujimori Kogyo, Kanagawa, Japan), which is a microchip flow chamber system, was used according to the protocol proposed by Hosokawa et al.[5,8] PTF evaluation was performed with type 1 collagen-coated platelet chip (Nitta Gelatin, Osaka, Japan). Briefly, the blood samples obtained were perfused into the capillary path of the microchip with a precision pump. The generated thrombi were placed over the surface area coated with collagen, and the resulting back pressure was monitored in real time using a pressure transducer placed on the upstream of the capillary. Thrombus formation was also recorded using a video microscope located under the microchip. For all participants, 350 μL of whole blood in the hirudin-anticoagulant tube was perfused into the platelet chips at flow rates of 12 μL min^{-1} (PL_{12}) and 24 μL min^{-1} (PL_{24}), which corresponded to high shear stress values of 1000 and 2000 s^{-1}, respectively. The flow pressure curves were assessed for 10 minutes. The PTF on the platelet chip's collagen surface was assessed quantitatively using the following variables: time to reach 5 kPa above the base pressure ($T_{5+\alpha}$), which indicated the onset of thrombus formation, and the area under the flow pressure curve for 10 minutes (AUC_{10}) <60 kPa, which quantified thrombus stability.

The clinical data of all children with Kawasaki disease included age, sex, blood count, serum biochemistry findings, hemostasis examination findings, IVIG resistance, and treatment with/without prednisolone and with/without CAL.

Statistical Analyses

Data were analyzed using the JMP10 (SAS Institute Inc, Cary, North Carolina). Results were presented as median (IQR). The Shapiro-Wilk test was used to evaluate normality. Between-group differences were compared using the Wilcoxon rank-sum test. Multiple comparisons of the different patient groups were conducted using the Kruskal-Wallis H test, also known as 1-way ANOVA. The groups were compared with the *t* test or Mann-Whitney *U* test, and the relationships between 2 variables were evaluated using Spearman rank correlations. *P* value of <.05 was considered statistically significant.

Results

Thirty-three pediatric patients with Kawasaki disease (25 male) were eligible in this study. Table I and Figure 1 show the clinical characteristics and clinical course. The age of onset ranged from 3 to 149 (median 27) months. In total, 16 (48%) patients received oral aspirin (n = 13, moderate dose and n = 3, low dose), and 17 (52%) patients initially received oral flurbiprofen because of elevated liver enzyme levels or during an influenza epidemic. All patients received IVIG therapy (n = 18; 2 g/kg for a day, n = 15; 1 g/kg for 2 days). Seven patients received IVIG therapy along with oral prednisolone. Ten (30%) patients did not respond to IVIG therapy (nonresponders) and subsequently received additional IVIG. Three patients were

Table I. Characteristics of patients with Kawasaki disease

Patients (n)	33 (100%)
Sex (male/female) (n)	25/8 (76/24%)
Median age at onset (mo)	27 [10.5-54.5]
Treatment with IVIG (n)	33 (100%)
2 g/kg for 1 d/1 g/kg for 2 d	18/15 (55/45%)
Nonresponder for IVIG (n)	10 (30%)
Antiplatelet drug (n)	33 (100%)
Aspirin at first	16 (48%)
Flurbiprofen at first	17 (52%)
Steroid (n)	5 (21%)
CAL (n)	2 (6%)
Control	
Adult control (n)	19
Child control (n)	11
Febrile control (n)	5

Values are median [IQR].

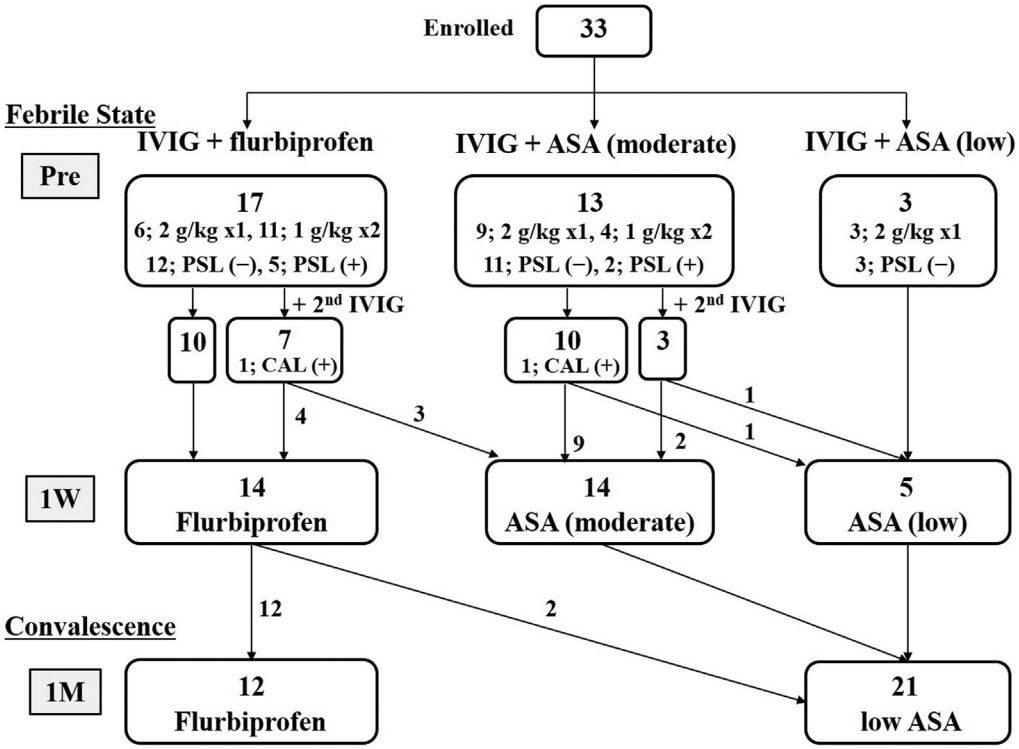

Figure 1. Selected treatment regimen and their outcomes in children with acute Kawasaki disease. *Moderate- or low-dose ASA*, moderate or low-dose aspirin; *PSL*, prednisolone; *Pre*, before treatment; *1 week*, 1 week after the start of treatment; *1 month*, 1 month after the start of treatment.

switched to moderate-dose aspirin because they had decreased liver enzyme levels. After the afebrile state, low-dose aspirin was prescribed if the patient did not present with influenza virus. Two patients developed CAL, and transient dilation returned to normal within 1 month of onset.

Using the PL_{12} video microscope, the early initiation of PTF at 1 minute in patients with Kawasaki disease was confirmed. However, at 7 minutes, the platelet thrombi could be easily flushed, indicating weak stability (**Video**; available at www.jpeds.com).

In children with Kawasaki disease, adult controls, child controls, and febrile controls, the pressure curves of PL_{12} and PL_{24} are depicted in **Figure 2**, A and B. At Pre, the median PL_{12}-$T_{5+\alpha}$ and PL_{24}-$T_{5+\alpha}$ were 3.3 minutes (IQR 2.0-4.5) and 1.3 minutes (0.9-1.9), respectively, in children with Kawasaki disease. Both values were significantly shorter than those of adult controls (3.5 minutes [2.9-6.4] and 2.8 minutes [1.8-4.8]; $P = .015$ and $P < .001$, respectively). Furthermore, the PL_{12}-AUC_{10} and PL_{24}-AUC_{10} were 151.7 U (94.5-279.9) and 359.4 U (235.0-453.3), respectively. The PL_{12}-AUC_{10} significantly decreased in adult controls (234.1 U [110.5-306.5], $P = .007$). In child controls, the PL_{24}-$T_{5+\alpha}$ was shorter (2.2 minutes [1.2-4.7], $P = .004$), and the PL_{12}-AUC_{10} decreased (234.3 U [94.9–414.8], $P = .002$). However, in febrile controls, there was no statistically significant difference in any of the variables (**Figure 2**, C). These findings showed that acute Kawasaki disease was characterized by the early onset and weak stability of PTF.

To assess the change in PTF during the clinical course of patients with Kawasaki disease, the pressure curves of PL_{12} and PL_{24} at Pre, 1 week, and 1 month after the start of treatment in all cases are shown in **Figure 3**, A. At 1 week and 1 month after the start of treatment, a pressure level of 5 kPa+α was not achieved in almost all cases. The recording at >10 minutes was considered as the maximum (∞ minutes), and the inverse of the maximum measure was approximately zero. Therefore, the inverse of $T_{5+\alpha}$ ($T_{5+\alpha}{}^{-1}$) was used for statistical analysis. The PL_{12}-$T_{5+\alpha}{}^{-1}$ were 0.31 (0.26-0.49) min^{-1} at Pre, 0.00 (0.00-0.37) min^{-1} at 1 week after the start of treatment, and 0.00 (0.00-0.29) min^{-1} at 1 month after the start of treatment. Meanwhile, the PL_{24}-$T_{5+\alpha}{}^{-1}$ were 0.76 (0.52-1.12) min^{-1} at Pre, 0.18 (0.00-1.03) min^{-1} at 1 week after the start of treatment, and 0.00 (0.00-0.59) min^{-1} at 1 month after the start of treatment. The $T_{5+\alpha}{}^{-1}$ at 1 week and 1 month after the start of treatment were lower than that at Pre under both shear values ($P < .001$, **Figure 3**, B). The PL_{12}-AUC_{10} were

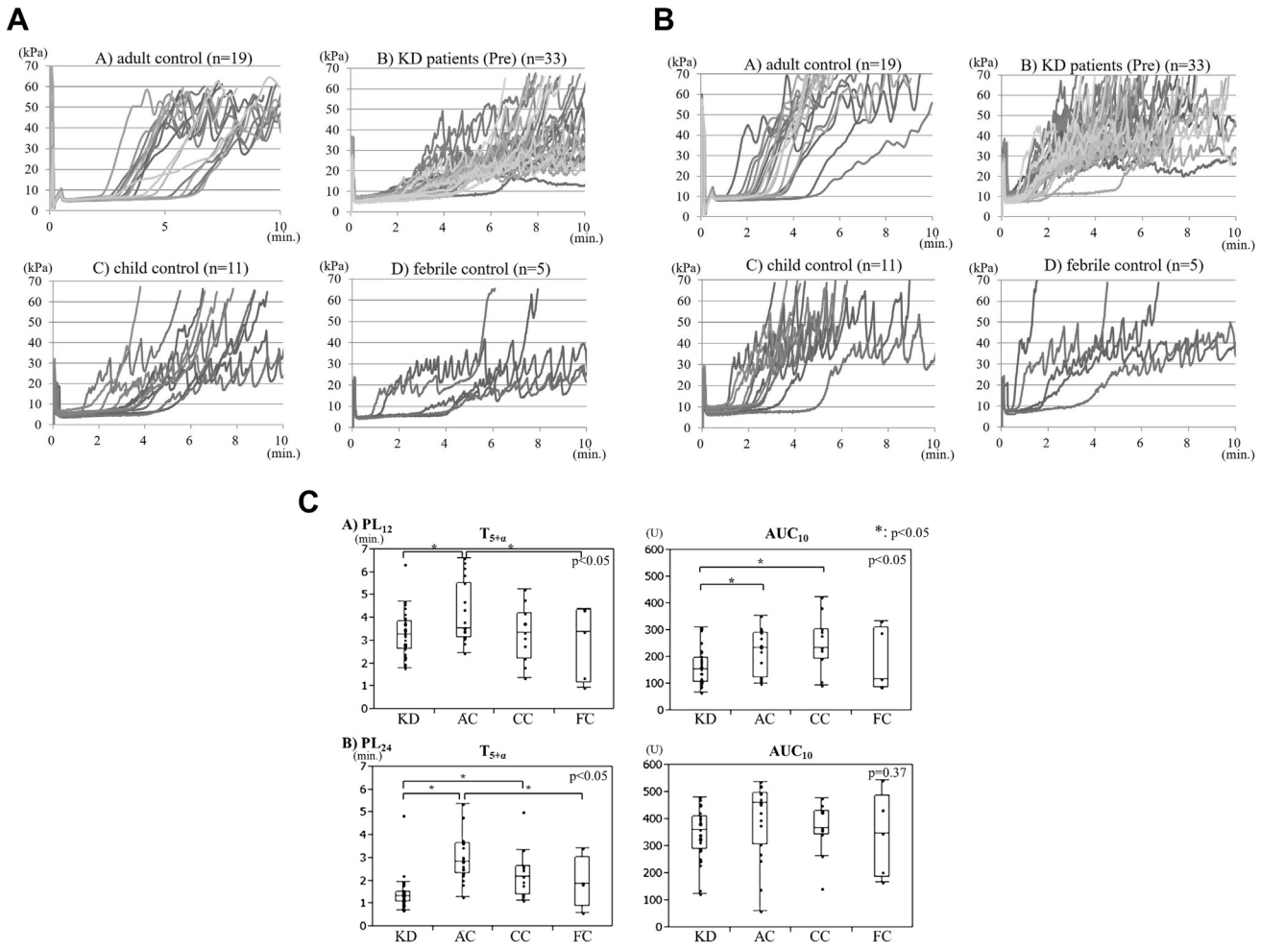

Figure 2. Pressure curve and comparison of the measures using the T-TAS-based assay between adult controls, child controls, febrile controls, and patients with acute Kawasaki disease during pre-treatment. **A,** and **B,** PL_{12} and PL_{24} assays, respectively, in adult controls, patients with Kawasaki disease (Pre), child controls, and febrile controls. **C,** Comparison of the measures for PTF characteristics under different flow conditions (PL_{12}, PL_{24} under high shear values [1000 and 2000 s^{-1}, respectively]) between patients with acute Kawasaki disease and controls. *P* value of <.05 was considered statistically significant. *AC*, adult control; *CC*, child control; *FC*, febrile control; *KD*, Kawasaki disease; $T_{5+\alpha}$; time to reach 5 kPa above the based pressure (α).

43.5 U (10.1-273.3) at 1 week and 11.4 U (2.6-323.1) at 1 month after the start of treatment, and the PL_{24}-AUC_{10} were 20.1 U (6.6-135.4) at 1 week and 7.0 U (2.1-120.7) at 1 month after the start of treatment. The AUC_{10} at 1 week and 1 month after the start of treatment decreased under both shear values ($P < .001$, Figure 3, B).

We investigated additional biochemical data to assess the correlation between the primary variables of interest. At Pre (Table II), although a high PL_{24}-AUC_{10} was associated with high red blood cell count and low brain natriuretic peptide level, most variables, including platelet counts, were not correlated with $T_{5+\alpha}$ and AUC_{10} under both shear values. Although the onset of PTF in patients treated with steroid was unlikely to be inhibited after treatment and antiplatelet therapy (Table III), most variables, including platelet counts, were not associated with ${T_{5+\alpha}}^{-1}$ and AUC_{10} under both shear values. There were no statistically significant differences in the effect of aspirin at different dosages or use of alternative drugs at any phase.

Discussion

The current study showed that the acute phase of Kawasaki disease was characterized by the early onset and weak stability of PTF. However, no statistically significant differences were observed in either $T_{5+\alpha}$ or AUC_{10} between patients with acute Kawasaki disease and febrile child controls. Thus, PTF characteristics under a high shear condition in children with Kawasaki disease were not specific.

T-TAS can be used to monitor the PTF process in whole blood mediated by platelet-collagen interaction under selected shear values in a condition similar to the in vivo condition. Moreover, the device has been already used to assess the efficacy of antiplatelet or anti-thrombotic therapy[9,10]

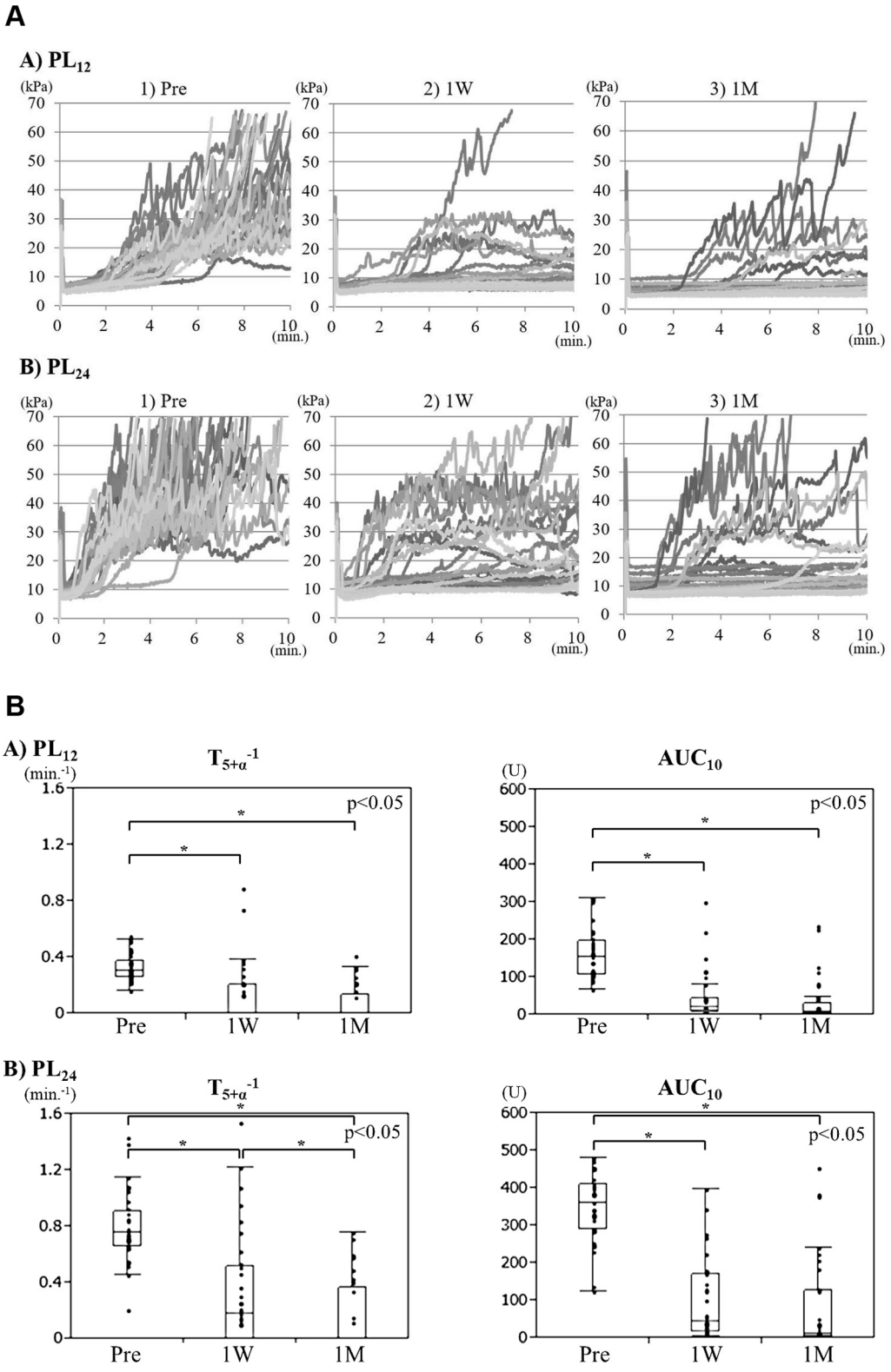

Figure 3. Changes in PTF at Pre, 1 week, and 1 month as assessed using the T-TAS in patients with acute Kawasaki disease. **A,** The pressure curves of the PL_{12} and PL_{24} chip assays at Pre, 1 week, and 1 month. **B,** Comparison of PTF measures under different flow conditions during Kawasaki disease treatment combined with antiplatelet therapy. *P* value of <.05 was considered statistically significant.

Table II. Relationship of clinical and biochemical variables with $T_{5+\alpha}$ necessary in the acute phase of Kawasaki disease

Variables	n	Median [IQR]	PL_{12}-$T_{5+\alpha}$ Correlation coefficient	*P*	PL_{24}-$T_{5+\alpha}$ Correlation coefficient	*P*	PL_{12}-AUC_{10} Correlation coefficient	*P*	PL_{24}-AUC_{10} Correlation coefficient	*P*
Age, mo	33	27 [10.5-54.5]	0.1552	.3884	−0.0601	.7399	−0.1649	.3592	−0.0532	.7689
male:female	33	25:8		.3272		.9441		.3559		.8401
γ-globulin responder: nonresponder	33	23:10		.066		.4038		.4876		.9879
steroid nonused: used	33	26:7		.7446		.9738		.304		.5702
CAL (−): (+)	33	31:2		.9993		.9929		.2667		.5154
WBC (/uL)	33	12 860 [10 660-20 050]	0.0833	.6451	0.062	.7319	0.0371	.8376	0.078	.6659
Neut (%)	33	71.8 [60.6-85]	0.2286	.2006	−0.82	.6503	−0.0592	.7436	−0.1088	.5467
RBC ($\times 10^4$/uL)	33	429 [405.5-456.5]	−0.1534	.3941	0.0952	.5981	0.3159	.0733	**0.4998**	**.0086**
Plt ($\times 10^4$/uL)	33	32.5 [26.7-40.1]	−0.0522	.7731	0.0832	.6453	0.2599	.1441	0.24	.1785
TP (g/dL)	32	6.6 [6.1-6.9]	−0.0288	.8757	0.2943	.1021	0.1535	.4016	0.3015	.0935
Alb (g/dL)	31	3.9 [3.5-4.1]	−0.1257	.5005	−0.0183	.9223	0.3328	.0673	0.3429	.0589
GOT (IU/L)	33	36 [24-87]	−0.0206	.9095	0.0032	.986	0.0003	.9985	−0.1211	.5020
GPT (IU/L)	33	26 [12-142.5]	−0.1332	.4599	−0.0592	.7436	−0.1828	.3085	−0.1961	.2742
Cre (mg/dL)	33	0.25 [0.21-0.32]	−0.0802	.6571	0.0907	.6158	−0.2376	.183	−0.1316	.4655
Na (mEq/L)	33	134 [132-136]	−0.0323	.8583	0.1427	.4281	−0.1054	.5592	−0.0908	.6154
PT (s)	15	14.3 [13-15.2]	0.0466	.8691	0.3199	.2451	0.3166	.2502	0.3435	.2101
APTT (s)	15	35.6 [31.4-37]	0.0385	.8917	0.3593	.1884	0.322	.2418	0.0659	.301
FDP	13	4.7 [3.7-5.5]	−0.3939	.1829	−0.2083	.4947	−0.2672	.3775	−0.0248	.9359
D-dimer (ug/mL)	18	1.4 [1.1-1.5]	−0.2998	.2268	−0.0668	.7924	−0.295	.2347	−0.3096	.2113
CRP (mg/dL)	33	7.9 [4.0-10.0]	0.0652	.7185	−0.181	.3135	−0.2367	.1848	−0.3219	.0677
BNP (mol/mL)	13	29.6 [18.5-190.7]	−0.3384	.2581	0.3752	.2065	−0.5309	.0619	**−0.5777**	**.0387**
vWF-AG	21	246.2 [140.2-304.9]	−0.0461	.8426	−0.1614	.4847	0.2286	.319	0.3052	.1785

Bold values indicate $P < .05$.

Alb, albumin; *APTT*, activated partial thromboplastin time; *BNP*, brain natriuretic peptide; *Cre*, creatinine; *CRP*, C-reactive protein; *FDP*, fibrin degradation product; *GOT*, glutamic oxaloacetic transaminase; *GPT*, glutamic pyruvic transaminase; *Na*, sodium; *Neut*, neutrophil; *Plt*, platelet count; *PT*, prothrombin time; *RBC*, red blood cell count; *TP*, total protein; *VWF:Ag*, VWF antigen; *WBC*, white blood cell count.

and hemodilution during cardiopulmonary bypass.[11] A previous study used T-TAS in patients receiving aspirin treatment. Results showed that the AUC_{10} decreased in a dose-dependent manner, and the effect of aspirin on time to reach 10 kPa (T_{10}), defined as PTF onset, was relatively minimal, thereby resulting in an unstable PTF under all examined shear stress values. By contrast, the use of abciximab decreased the AUC_{10} by prolonging T_{10} in a

Table III. Relationship of clinical and biochemical variables with $T_{5+\alpha}{}^{-1}$ necessary in the acute phase of Kawasaki disease

Variables	n	Median [IQR]	PL_{12}-$T_{5+\alpha}{}^{-1}$ Correlation coefficient	*P*	PL_{24}-$T_{5+\alpha}{}^{-1}$ Correlation coefficient	*P*	PL_{12}-AUC_{10} Correlation coefficient	*P*	PL_{24}-AUC_{10} Correlation coefficient	*P*
1 wk after starting treatment										
the antiplatelet therapy moderate ASA: low ASA: flurbiprofen	33	14:5:14		.2661		.1799		.3878		.1262
γ-globulin responder: nonresponder	33	23:10		.6531		.3937		.5975		.4132
steroid nonused: used	33	26:7		.4168		**.0431**		.4356		.0627
CAL (−):(+)	33	31:2		.8957		.5449		.6552		.3931
WBC (/uL)	33	9500 [7615-14 200]	0.3167	.0725	0.3153	.0739	0.3142	.0749	0.3421	.0513
Neut (%)	12	32 [25.5-66.6]	0.1334	.6794	0.2361	.4601	0.3818	.2207	0.3573	.2542
RBC ($\times 10^4$/uL)	33	436 [396-463]	−0.0908	.6154	−0.159	.3769	−0.2283	.2012	−0.1302	.4701
Plt ($\times 10^4$/uL)	33	53 [41.9-71.6]	0.2211	.2163	−0.0431	.8119	0.0856	.6359	0.0458	.8002
1 mo after treatment										
the antiplatelet therapy low ASA: flurbiprofen	33	21:12		.7452		.9491		.2337		.5928
γ-globulin responder: nonresponder	33	23:10		.4371		.5923		.1863		.7044
steroid nonused: used	33	26:7		.0968		.0558		.1399		.0765
CAL (−):(+)	33	31:2		.4242		.3601		.4971		.4052
WBC (/uL)	33	8200 [5995-11 120]	0.2393	.1798	0.3076	.0816	0.2093	.2425	0.1912	.2865
Neut (%)	11	29.6 [23.4-40.9]	−0.6012	.0504	−0.5159	.1043	−0.1727	.6115	−0.3636	.2716
RBC ($\times 10^4$/uL)	33	431 [421-462.5]	0.251	.1588	0.2125	.2351	0.1863	.2993	0.1976	.2702
Plt ($\times 10^4$/uL)	33	35.3 [30-43.6]	0.0079	.9653	−0.0368	.8387	0.0057	.975	−0.0628	.7283

dose-dependent manner.[12] These results indicate that aspirin's antiplatelet efficacy was mainly attributable to PTF's weakened stability, not by inhibiting PTF onset. By contrast, abciximab's efficacy was primarily caused by inhibiting PTF onset. Abciximab, a platelet glycoprotein (GP) IIb/IIIa receptor inhibitor, promotes vascular remodeling in Kawasaki disease,[9,10] and the mechanism of the GPIIb/IIIa receptor pathway can treat thrombi in patients with Kawasaki disease successfully.[13,14] The current antiplatelet therapy of acute Kawasaki disease in 1 week and 1 month by aspirin or flurbiprofen effectively suppressed platelet activation. Although antiplatelet drugs such as platelet GPIIb/IIIa receptor inhibitor would be reasonable for acute Kawasaki disease due to inhibiting the onset of PTF.

Based on a systematic search and review,[4] several studies have reported antiplatelet treatment's impact on Kawasaki disease. All studies have shown that platelet aggregation is more likely to decrease after antiplatelet treatment.[3,15-20] However, only 1 of the 7 studies had statistically significant results.[20] In the current study, no statistically significant differences were observed in the effect of aspirin at different dosages, at any phase, on $T_{5+\alpha}$ and AUC_{10} after antiplatelet therapy. In a previous study, the 6-keto-prostaglandin F1 alpha level decreased significantly in patients treated with high-dose aspirin compared with those treated with low-dose aspirin.[21] This contrasting result may be attributed to the presence of shear stress.

The current antiplatelet therapy by aspirin or flurbiprofen in acute Kawasaki disease effectively suppresses platelet activation. Considering the weak stability of PTF because of exhausted platelet activation, we would need antiplatelet therapy but not increased aspirin dosage.

A previous study compared the effect of 2 different dosages of aspirin plus IVIG, and the result showed that high-dose aspirin had minimal benefits compared with low-dose aspirin during treatment at the acute phase of Kawasaki disease.[22] Subsequently, a comparison of the use of aspirin in the acute stage revealed that high- or medium-dose aspirin had minimal benefits compared with treatment without aspirin.[23-26] In this study, PTF's early onset and weak stability in the acute phase of Kawasaki disease may support treating Kawasaki disease without aspirin.

The current study had several limitations. Only a small sample size was included, and a higher number of samples were difficult to obtain because analysis using T-TAS is generally performed within 4 hours after the collection of samples. Furthermore, the timing of sample collection was based on the time when the treatment was initiated, not by the day from the onset or the day when the fever subsided. Therefore, the cases at 1 week were indefinite as febrile or afebrile, and aspirin dosage. Other examinations for platelet activation, including multiple electrode aggregometry, were not performed owing to the lack of volume samples. However, PTF occurrence under a high shear stress condition in patients with acute Kawasaki disease was not reported.

Acute Kawasaki disease in children was characterized by PTF's early onset and weak stability. However, this was not specific to Kawasaki disease. Platelet activation was suppressed both at 1 week and 1 month after the start of treatment, and no significant difference was observed in the effect of aspirin at different dosages or the use of alternative drugs to suppress platelet activation. ■

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Reprint requests: Keiji Nogami, MD, PhD, Department of Pediatrics, Nara Medical University, 840 Shijo-cho, Kashihara, Nara 634-8522, Japan. E-mail: roc-noga@naramed-u.ac.jp

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