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Original article

Persistent high fever for more than 10 days during acute phase is a risk factor for endothelial dysfunction in children with a history of Kawasaki disease

Yasuhiko Mori (MD, PhD)[a,b], Hiroshi Katayama (MD, PhD, FJCC)[a,*], Kanta Kishi (MD, PhD)[a], Noriyasu Ozaki (MD)[a], Tatsuo Shimizu (MD, PhD)[c], Hiroshi Tamai (MD, PhD)[a]

[a] Department of Pediatrics, Osaka Medical College, Takatsuki, Japan
[b] Mori Kid's Clinic, Japan
[c] Department of Pediatrics, Hokusetsu General Hospital, Japan

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ABSTRACT

Background: Endothelial dysfunction has previously been reported in children with a history of Kawasaki disease, but the determinants of endothelial function in Kawasaki disease patients are still unknown. In this study, we investigated endothelial function in Kawasaki disease patients and attempted to identify risk factors for persistent endothelial dysfunction.

Methods: Using high-resolution ultrasound, we measured the percent flow-mediated dilatation, an arterial response to reactive hyperemia, to evaluate endothelial function in 67 patients with a history of Kawasaki disease and 28 age- and sex-matched control subjects. We divided the Kawasaki disease patients into a group with impaired endothelial function (the percent flow-mediated dilatation below −2 standard deviations of the control group) and a group with normal endothelial function (the percent flow-mediated dilatation more than −2 standard deviations of control). Logistic multiple regression analysis was performed to identify independent predictors of impaired endothelial function.

Results: In Kawasaki disease patients, the percent flow-mediated dilatation was significantly lower than in the control subjects (9.8 ± 3.6%, compared with 13.1 ± 3.4%, $p < 0.01$). In 13 Kawasaki disease patients (3 patients with coronary artery lesions and 10 patients without coronary artery lesions), the percent flow-mediated dilatation was below −2 standard deviations of control. Logistic multiple regression analysis showed that a febrile period of longer than 10 days during the acute phase was the significant risk factor for endothelial dysfunction (odds ratio: 8.562; 95% confidence interval: 1.366–53.68). Presence of coronary artery lesions was not a determinant of endothelial dysfunction.

Conclusions: Systemic endothelial dysfunction exists in children with a history of Kawasaki disease, and a febrile period of longer than 10 days during the acute phase is an independent predictor of endothelial dysfunction irrespective of coronary artery involvement.

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Introduction

Kawasaki disease is an acute, febrile, pediatric illness that occasionally causes coronary artery lesions [1,2]. This disease is characterized by systemic vasculitis and may be a risk factor for the early progression of atherosclerosis in adolescents, although this has yet to be confirmed by epidemiological studies [3]. Endothelial dysfunction is one of the earliest changes in various types of vascular remodeling, including atherosclerosis [4]. Recently, endothelial function has been investigated noninvasively on the basis of systemic arterial reactivity. Several investigators have reported on the endothelial function of Kawasaki disease patients. Previous studies have demonstrated that systemic endothelial dysfunction exists in Kawasaki disease irrespective of coronary artery involvement [5], and is not influenced by early treatment with high-dose gamma globulin during the acute stage [6]. Because conflicting results have been reported about systemic endothelial function in Kawasaki disease patients [7,8], the actual determinants of endothelial function in this disease are still unknown. In the present study, therefore, we investigated the endothelial

* Corresponding author at: Department of Pediatrics, Osaka Medical College, 2-7 Daigaku-cho, Takatsuki 569-8686, Japan. Tel.: +81 72 683 1221; fax: +81 72 684 5798.
E-mail address: ped100@poh.osaka-med.ac.jp (H. Katayama).

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function of Kawasaki disease patients and attempted to identify risk factors for persistent endothelial dysfunction.

Methods

Subjects

We studied 67 children with a history of Kawasaki disease (36 boys and 31 girls aged 9.7 ± 2.5 years at examination; range: 6–15 years) and 28 sex- and age-matched controls (16 boys and 12 girls aged 8.6 ± 2.2 years; range: 4–13 years). Subjects with evidence of risk factors for cardiovascular disease such as smoking, hyperlipidemia, hypertension, and diabetes mellitus were excluded. Kawasaki disease was diagnosed from the standard criteria defined by the Japanese Ministry of Health and Welfare. The mean duration from the onset of Kawasaki disease to examination was 7.5 ± 2.4 years. Among the 67 Kawasaki disease patients, in the first month after onset of Kawasaki disease, the maximal coronary artery involvement as noted on echocardiography was described as coronary artery lesions (more than 2 standard deviations above normal and more than 3 mm in diameter) in 10 patients. All subjects refrained from consuming antioxidant-containing foods and beverages, such as Japanese and English tea, fruit juice, and vitamin supplements for at least 24 h before examination. This study was approved by the local ethics committee, and informed consent was obtained from the parents of all subjects.

Study design

We took a history from each subject, and performed a physical examination, including the height, weight, and supine blood pressure. The medical records of the Kawasaki disease patients were reviewed to ascertain the details of the acute illness. Total cholesterol and triglyceride levels were measured in all subjects, and high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, random blood glucose, immunoreactive insulin, and *Chlamydia pneumoniae* antibody titers were measured in the Kawasaki disease patients. Blood samples were obtained after an overnight fast. Brachial artery endothelial function was investigated as described below.

Measurement of brachial artery endothelial function

We determined endothelium-dependent flow-mediated dilation and hyperemic flow of the brachial artery in a quiet and temperature-controlled room, as described previously [9]. The same examiner performed all examinations throughout the study. The diameter of the brachial artery was measured on two-dimensional ultrasound images that were acquired using a 7.0 MHz linear array transducer and a Hewlett-Packard (Palo Alto, CA, USA) Sonos 5500. To determine the baseline diameter, the brachial artery was scanned longitudinally at 2–10 cm above the elbow after the subject had rested for at least 10 min. After inflating a pneumatic tourniquet distal to the target arterial segment and holding the pressure at 250 mm of mercury for 4–5 min, scanning was repeated at 30 s before and 90 s after cuff deflation. Flow velocity was measured using a pulsed Doppler signal at 70° to the vessel wall, with the range gate (1.5 mm) set at the center of the artery. Flow measurements were recorded during the first baseline scan and again during the first 15 s of reactive hyperemia, and the increase in flow was expressed as a percentage of baseline flow. The electrocardiograph was monitored continuously throughout the study. All recordings were stored on super-video home system videotape for later analysis.

Measurements of the arterial diameter and blood flow were made from the videotapes by a single observer who was blinded to the clinical details and stage of the experiment. The arterial diameter was measured from the anterior to posterior "m-line" at end-diastole, coinciding with the R wave on the electrocardiograph. Four cardiac cycles were analyzed for each scan. Diameter measurements were also obtained at 50–60 s after cuff deflation to assess the effect of reactive hyperemia and the change in diameter was calculated as a percentage relative to the baseline diameter. The baseline diameter was subtracted from the diameter after cuff deflation, the result of which was then divided by the baseline diameter and multiplied by 100, yielding the percent flow-mediated dilatation.

Statistical analysis

Descriptive data are presented as the mean value (±standard deviation) unless otherwise specified. Differences of the percent flow-mediated dilatation between the Kawasaki disease patients and control subjects were analyzed by the unpaired Student's *t*-test.

We divided the Kawasaki disease patients into two groups, which were impaired endothelial function (the percent flow-mediated dilatation below −2 standard deviations of control) and normal endothelial function (the percent flow-mediated dilatation more than −2 standard deviations of control). Differences between these groups were assessed by the unpaired Student's *t*-test for continuous variables and by the χ^2-test for categorical variables.

Furthermore, logistic multiple regression analysis was performed to identify independent predictors of impaired endothelial function. The variables analyzed were age at the examination, coronary artery lesions, low-density lipoprotein cholesterol, immunoreactive insulin, and febrile (temperature more than 37.5°) period during the acute phase of Kawasaki disease. Statistical significance was accepted at a p value less than 0.05.

Results

The Kawasaki disease patients and the control subjects were well matched for age, gender, and body mass index. Total cholesterol and triglyceride levels did not differ between the Kawasaki disease patients and the control subjects (Table 1).

There were no qualitative differences between the two groups with regard to the appearance of the vessel walls or intima. There were also no significant between-group differences of baseline brachial artery diameter or the increase in flow during reactive hyperemia. However, the percent flow-mediated dilatation of the brachial artery was significantly smaller in the Kawasaki disease patients than in the controls (9.8 ± 3.6%, compared with 13.1 ± 3.4%, $p < 0.01$) (Table 1, Fig. 1). The percent flow-mediated dilatation of the Kawasaki disease patients without coronary artery

Table 1
Characteristics and vascular studies in Kawasaki disease patients and control subjects.

	Kawasaki patients (n = 67)	Control subjects (n = 28)	p value
Age, year	9.7 (2.5)	8.6 (2.2)	NS
Gender, male/female	36/31	16/12	NS
Body mass index, kg/m^2	17.2 (2.5)	17.4 (3.5)	NS
Total cholesterol, mg/dl	177.6 (29.3)	168.5 (36.3)	NS
Triglyceride, mg/dl	56.8 (37.7)	59.1 (31.8)	NS
Random blood glucose, mg/dl	91.9 (7.3)	96.3 (17.3)	NS
Vessel size, mm	2.8 (0.4)	2.6 (0.3)	NS
Reactive hyperemia, %	257 (77)	268 (69)	NS
Flow-mediated dilation, %	9.8 (3.6)	13.1 (3.4)	Less than 0.01

Values are mean (standard deviation).
n, number of patients or subjects; NS, not significant.

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