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Vascular Health in Kawasaki Disease

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Objectives The objective of our study was to compare the indices of vascular health in Kawasaki disease (KD) patients to those of control subjects.

Background The literature on peripheral vascular health after KD is conflicting.

Methods Subjects were patients 11 to 29 years of age with the onset of KD >12 months before the study visit (n = 203) and healthy control subjects (n = 50). We measured endothelial function (using the Endothelial Pulse Amplitude Testing index), intima-media thickness (IMT) of the right common carotid artery (RCCA) and the left common carotid artery (LCCA), and fasting lipid profile and C-reactive protein (CRP). KD patients were classified according to their worst-ever coronary artery (CA) status: group I, always normal CAs (n = 136, 67%); group II, CA *z*-scores ≥2 but <3 (n = 20, 10%); group III, CA aneurysm *z*-scores ≥3 but <8 mm (n = 40, 20%); and group IV, giant CA aneurysm, defined as ≥8 mm (n = 7, 3%).

Results At a median of 11.6 years (range, 1.2 to 26 years) after KD onset, compared with controls, KD patients had a higher peak velocity in the LCCA (p = 0.04) and higher pulsatility index of both the RCCA and LCCA (p = 0.006 and p = 0.05, respectively). However, there were no differences in the Endo-PAT index or carotid IMT or stiffness. The mean IMT of the LCCA tended to differ across the KD subgroups and control group (p = 0.05), with a higher mean in group IV. Otherwise the KD subgroups and control group had similar vascular health indexes.

Conclusions In contrast to some earlier reports, our study of North American children and young adults demonstrated that KD patients whose maximum CA dimensions were either always normal or mildly ectatic have normal vascular health indexes, providing reassurance regarding peripheral vascular health in this population. (J Am Coll Cardiol 2013;62:1114–21) © 2013 by the American College of Cardiology Foundation

Kawasaki disease (KD) is an acute, self-limited vasculitis of unknown etiology that occurs predominantly in infants and young children. First described in 1967 in Japan, the disease is now known to occur throughout the world in children of all races and ethnicities (1). Indeed, in developed countries, KD has now surpassed acute rheumatic fever as the leading cause of childhood acquired heart disease and accounted for 4,000 hospitalizations in the United States in 2000 (2,3). Treatment of KD in the acute phase is aimed at reducing inflammation in the coronary artery (CA) wall and preventing coronary thrombosis. CA aneurysms or ectasia develop in ~20% to 25% of untreated children with the disease and may lead to myocardial infarction, sudden death, or ischemic heart disease (4). Administration of high-dose intravenous gamma globulin within the first 10 days of illness lowers the risk of CA aneurysms to ≤5% and of giant aneurysms to 1% (5).

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Patients with persistent aneurysms have systemic inflammation years after disease onset, as evidenced by C-reactive protein (CRP) levels that are significantly higher than those seen in healthy children (6,7). Studies in these patients with persistent CA lesions have demonstrated endothelial dysfunction (8–10). In patients with persistent aneurysms, the carotid intima-media thickness (IMT) also has been found to be thicker than in control patients (8). Similar findings have been observed in KD patients with regressed

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aneurysms (11,12). The data, however, are conflicting in KD patients without a history of CA dilation (9,12,13).

To assess the determinants of vascular function, we performed a single-center study in a population of North American adolescents and young adults with a history of KD. CA lesions and medical history were meticulously characterized. We used different modalities to assess vascular health, including endothelial function testing and carotid ultrasound.

Methods

Subjects. We studied patients with KD followed at Boston Children's Hospital in whom KD onset occurred at least 12 months before the study visit and whose current age was 11 to 29 years. Control subjects of similar age and sex were recruited through community listing. Exclusion criteria for both KD and control subjects included a history of structural heart disease, latex allergy, and the presence of a condition that might affect vascular function such as rheumatological disease, diabetes, and other chronic medical conditions. Vascular testing was deferred for at least 4 weeks in subjects with acute illness (i.e., febrile illness or viral syndromes). Signed consent was obtained from a parent or guardian for patients younger than 18 years of age or from the participant when 18 years of age or older. Participants younger than 18 years of age gave assent. The study was approved by the institutional review board of the Boston Children's Hospital.

Testing. Subjects were asked to fast overnight for 12 h except for the consumption of water. The subject's weight and height were measured using a Scale-Tronix 5002 stand-on scale (Scale-Tronix, Wheaton, Illinois) and a SECA 240 mechanical, high-precision measuring rod (Seca, Hamburg, Germany). Blood pressure was measured on the dominant arm in the sitting position using the oscillometric method (Dinamap, GE, Waukesha, Wisconsin) after at least 5 min of resting. Four blood pressure measurements were obtained, and measurements 2 through 4 were averaged.

ENDOTHELIAL PULSE AMPLITUDE TESTING. The Endothelial Pulse Amplitude Test (Endo-PAT) is a U.S. Food and Drug Administration–approved device that is based on the principle of reactive hyperemia. It has been validated in adults and studied in several high-risk pediatric groups (14–18). A lower Endo-PAT index indicates worse CA health. The Endo-PAT testing protocol, as described previously (14) (Itamar Medical Ltd, Caesarea, Israel) was performed in the morning or early afternoon (starting time between 7:30 AM and 11:30 AM). The Endo-PAT data were analyzed with the proprietary software package, without any input from the examiner. The Endo-PAT index was defined as the ratio of the average pulse amplitude during the 1-min period beginning after exactly 90 s of reactive hyperemia compared with the average pulse amplitude during the 210-s pre-occlusion baseline period. We have shown excellent feasibility and reproducibility of this modality in healthy adolescents previously (14). Participants were asked to grade discomfort/pain immediately after the test was completed.

CAROTID ULTRASOUND. We performed carotid ultrasound examinations to detect structural and functional arterial abnormalities in the carotid arteries. Increased thickness of the intimal-medial portion of the carotid artery is a marker of the presence of atherosclerosis (19). In addition, carotid arterial stiffness demonstrated by ultrasonography has been reported to be associated with cardiovascular events (20). Recently, Doppler ultrasound has been used as a method to evaluate not only significant stenosis or plaque formation but also hemodynamic alterations in the common carotid artery (CCA) in hypertensive patients (21). The right CCA (RCCA) and left CCA (LCCA) were examined in longitudinal and transverse planes using high-resolution B-mode gray-scale and color duplex ultrasonography (22). The carotid IMT of the far wall of the artery was measured in anterior, posterior, and lateral angulations in a zoomed mode across a 1-cm segment at the distal end of the CCA, proximal to the carotid bulb. Edge detection software was used (iE33 system, Q lab, Philips, Andover, Massachusetts). A pulsed-wave Doppler sample was placed in the CCA and internal carotid artery for systolic and diastolic velocity acquisition and to measure the pulsatility index ([peak systolic velocity − minimum diastolic velocity]/mean velocity) (23). Cross-sectional dimensions of the CCA in systole and diastole were measured in triplicate and averaged to calculate the arterial pressure–strain elastic modulus (24). The ultrasound probes were calibrated for axial and lateral resolution using an ultrasound phantom to ensure accuracy and consistency of measurements. The inter- and intraobserver percentages of error for carotid IMT measurement were <2%. The inter-observer intraclass correlation coefficients for pressure–strain elastic modulus were 0.828 (95% confidence interval: 0.566 to 0.932) and 0.778 (95% confidence interval: 0.439 to 0.912) for the RCCA and LCCA, respectively.

LABORATORY ANALYSIS. Fasting lipid profile (total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels), and CRP level were collected on the day of the visit after the vascular tests were completed.

LIFESTYLE AND DIET. A set of questionnaires about each patient's lifestyle and clinical and family history was completed on the day of the visit. A dietary recall of all food, beverages, vitamins, and supplements consumed by the subjects in the 24 h preceding testing was obtained. Subjects were also asked to report any exercise or physical activity performed in the 24 h preceding testing. These data were

Abbreviations and Acronyms

CA = coronary artery
CCA = common carotid artery
CRP = C-reactive protein
Endo-PAT = Endothelial Pulse Amplitude Testing
IMT = intima-media thickness
KD = Kawasaki disease
LCCA = left common carotid artery
RCCA = right common carotid artery

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Table 1 Demographics

	KD Group (n = 203)	Control Group (n = 50)	p Value
Age at testing, yrs	16.73 ± 4.21	17.57 ± 4.33	0.22
Male	122 (60%)	29 (58%)	0.87
Height, cm	166 (136–195)	165 (148–188)	0.55
Weight, kg	61 (29–123)	60 (39–109)	0.70
Body mass index, kg/m^2	22.74 ± 4.81	21.94 ± 3.81	0.21
Body surface area, m^2	1.70 ± 0.29	1.69 ± 0.22	0.72
Blood pressure, mm Hg			
Systolic	118 ± 12.53	117 ± 13.15	0.56
Diastolic	72 ± 9.05	70 ± 9	0.12
Mean	84 ± 9	80 ± 10	0.02
Sex by age group			0.91
11 to 19 yrs	161 (102 male, 50%)	38 (23 male, 46%)	
20 to 29 yrs	42 (20 male, 10%)	12 (6 male, 12%)	
Days from last menstrual cycle to testing (n = 64, n = 19)	19 (0–375)	14 (2–35)	0.43
Race			0.39
White	162 (80%)	38 (76%)	
Black/African American	11 (5%)	5 (10%)	
Asian	18 (9)	4 (8%)	
Multiple races	5 (2%)	2 (4%)	
Other	1 (<1%)	1 (2%)	
Unknown	6 (3%)	0 (0%)	
Ethnicity			0.68
Hispanic	12 (6%)	2 (4%)	
Non-Hispanic	187 (92%)	48 (96%)	
Smoker	6 (3%)	3 (6%)	0.39

Values are mean ± SD, n (%), or median (range).
BMI = body mass index; BSA = body surface area; KD = Kawasaki disease.

analyzed with Elizabeth Stuart Hands and Associates software, version 10.1 (Salem, Oregon) to assess for average daily intake of saturated and unsaturated fats and select vitamins, as these factors are known to affect endothelial function. Subjects reported a detailed clinical medical history including current medications, vitamins, and supplements. Subjects were asked to report all regular physical activity performed during the year before testing. We categorized activity as vigorous or moderate using the reference list of metabolic equivalents by Ainsworth et al. (25). Activities with metabolic equivalent values of ≥6 were classified as vigorous. Subjects were also asked to give a detailed summary of the number of hours they spent doing sedentary activities such as quiet play, computer time, television time, and reading/homework in the week before testing as well as the average number of hours spent sleeping each night in the past year.

CLINICAL AND FAMILY HISTORY. Additional clinical medical data were gathered from subjects' medical records including details about the acute phase of the disease, such as the date of fever onset, KD symptoms, treatment, and CA status. In addition, participants reported family history for first- and second-degree relatives.

Statistical analysis. Patient characteristics including demographic information, lipid profile, nutrition information, exercise variables, and vascular testing results were compared for the KD and control groups using the Fisher exact test for categorical variables and either the Wilcoxon rank sum test or unpaired *t* test for continuous variables. Continuous variables are presented as mean ± SD if the values were normally distributed and median (range) if not normally distributed, unless otherwise noted. The primary outcome variable was the Endo-PAT index. Analyses of all other vascular testing variables are considered exploratory; the p values presented have not been adjusted for multiple comparisons. Additional analyses were performed categorizing KD patients into 4 subgroups by their worst-ever CA status; comparisons of continuous variables were made using either the Kruskal-Wallis test or 1-way analysis of variance. Patients were classified according to their worst-ever CA status: group I, always normal CAs; group II, CA *z*-scores ≥2 but <3; group III, CA *z*-scores ≥3 but <8 mm; and group IV, giant CA aneurysm (≥8 mm) (26). The *z*-scores were based on the dimensions of the proximal left anterior descending or proximal right CA (26). In a secondary analysis in which CA dimensions were classified only according to the *z*-score, group III included patients with CA *z*-scores ≥3 but <10, and group IV (giant aneurysms) included patients with CA *z*-scores of ≥10 (27). In addition we analyzed the data omitting any patient who admitted to smoking.

Results

Demographics. KD patients did not differ significantly from the control group in age, body size, systolic and

diastolic blood pressure, sex, race, or ethnicity (Table 1). The mean blood pressure in the KD group was higher than that in the control group (84 ± 9 mm Hg vs. 80 ± 10 mm Hg, p = 0.02). The groups also had similar lipid profiles, CRP levels, and other medical history data, including variables related to smoking, 24-h nutrition, and exercise (Table 2). There was a trend toward increased CRP levels in the KD group (0.1 mg/dl [range, 0.1 to 3.1 mg/dl] vs. 0.1 mg/dl [range, 0.1 to 0.4 mg/dl], p = 0.06). The control group, compared with the KD group, included a greater percentage who had smoked within 24 h before testing (10% vs. 1%, p = 0.001, 2 of these control subjects do not consider themselves smokers) and a lower percentage with a family history of hypertension (58% vs. 78%, p = 0.001).

KD history. The majority of the patients had typical KD (n = 187, 92%). Eight KD patients had atypical KD. In 8 patients who received their initial treatment at an outside hospital, the original clinical observations were unavailable. Intravenous gamma globulin was administered to 188 patients (93%) at a median of 6 days (range, 0 to 23 days) from fever onset. Table 3 classifies the patients by their worst-ever and current CA status. When classified by their worst-ever status, KD patients included 136 (67%) in group I, 20 (10%) in group II, 40 (20%) in group III, and 7 (3%) in group IV. At a median of 11.6 years (range, 1.2 to 26 years) after KD onset, 10 of 203 patients (5%) had persistent CA aneurysms.

Table 2 Blood Work, Nutrition, and Exercise

	KD (n = 203)	Control (n = 50)	p Value
Lipid profile and CRP			
TC, mg/dl	153 (91–279)	151 (86–229)	0.34
HDL, mg/dl	53.7 (26.6–108.6)	53.6 (28.5–90.7)	0.63
TC/HDL	2.78 (1.36–5.36)	2.86 (2–4.82)	0.61
Triglycerides, mg/dl	67 (21–248)	65 (34–186)	0.99
LDL, mg/dl	85 (20–162)	87 (33–145)	0.59
CRP, mg/dl	0.1 (0.1–3.1)	0.1 (0.1–0.4)	0.06
Nutrition intake in the 24 h before testing			
Monosaturated fat, g	12 (0–184)	10 (0–73)	0.25
Polysaturated fat, g	5 (0–332)	4 (0–46)	0.24
Saturated fat, g	27 (1–184)	23 (1–101)	0.18
Omega 3, g	0.3 (0–37)	0.3 (0–6.1)	0.53
Omega 6, g	3 (0–295)	3 (0–45)	0.25
Vitamin A carotenoid (RE)	31 (0–6,737)	40 (0–3.596)	0.52
Vitamin E, mg	3 (0–80)	3 (0–60)	0.55
Beta-carotene, μg	117 (0–13,016)	109 (0–16,959)	0.82
Exercise activity in the year before testing			
Vigorous activity, h/week	6 (0–115)	4 (0–40)	0.57
Moderate activity, h/week	3 (0–42)	3 (0–15)	0.29
Sedentary activity (h/previous week)	30 (0–113)	33 (2–94)	0.37
Sleep, h/night	8 (0–12)	8 (4–13)	0.66

Values are median (range).

CRP = C-reactive protein; HDL = high-density lipoprotein cholesterol; KD = Kawasaki disease; LDL = low-density lipoprotein cholesterol; Omega 3 = omega 3 fatty acids; Omega 6 = omega 6 fatty acids; RE = retinol equivalent; TC = total cholesterol.

Table 3 Coronary Artery Status (n = 203)*

Worst ever	
No coronary artery enlargement (group I)	136 (67%)
Ectasia (*z*-score [>= sign] 2, but <3) (group II)	20 (10%)
Ectasia (*z*-score ≥3), aneurysm (<8 mm) (group III)	40 (20%)
Giant aneurysms (≥8 mm) (group IV)	7 (3%)
Current	
No coronary artery enlargement	156 (77%)
Ectasia (*z*-score [>= sign] 2, but <3)	2 (1%)
Ectasia (*z*-score ≥3), aneurysm (<8 mm)	4 (2%)
Giant aneurysms, ≥8 mm	6 (3%)
Regressed ectasia, aneurysms	35 (17%)

Values are n (%). *z-Scores are based on measurements of the proximal left anterior descending or proximal coronary arteries.

Vascular health testing. Table 4 summarizes the results of the vascular testing in the overall KD group and control group. No statistically significant difference was found for the primary outcome of Endo-PAT index. Compared with control subjects, KD patients tended to have higher peak velocity in the LCCA (127 ± 23 cm/s vs. 120 ± 20 cm/s, p = 0.04) and a higher pulsatility index of both the RCCA and LCCA (1.26 ± 0.36 vs. 1.13 ± 0.28, p = 0.006 and 1.23 ± 0.33 vs. 1.14 ± 0.27, p = 0.05, respectively). The groups did not differ significantly in the measures of endothelial function, in IMT of RCCA and LCCA, or in stiffness of the RCCA and LCCA. No plaques were identified in the patient or control group by carotid ultrasound. KD patients and controls reported a similar degree of discomfort after administration of Endo-PAT testing.

We also compared mean values on Endo-PAT testing and carotid ultrasound among the four KD subgroups and the control group (Table 5, Figs. 1 and 2). KD subgroups and control group had similar vascular health indices and CRP levels. Risk factors for atherosclerotic CA disease, including lipid profile, blood pressure and history of smoking, were equivalent within KD subgroups classified according to worst-ever CA status.

In further subgroup analyses, there were no significant differences in Endo-PAT and carotid ultrasound variables between the control group and either those with persistent aneurysms (combined groups III and IV) or those with giant aneurysms (group IV). When comparing patients with current CA aneurysms after KD (n = 10), no current CA aneurysms after KD (n = 191), and the control group (n = 50), KD patients without current CA aneurysms and KD patients with current CA aneurysms showed a trend toward increased LCCA IMT (0.459 ± 0.046 mm vs. 0.436 ± 0.033 mm vs. 0.434 ± 0.028 mm, p = 0.06, 1-way analysis of variance). This observation was similar in CRP levels (0.1 mg/dl [range, 0.1 to 3.1 mg/dl] vs. 0.1 mg/dl [range, 0.1 to 1.7 mg/dl] vs. 0.1 mg/l [range, 0.1 to 0.4 mg/dl], p = 0.06, Kruskal-Wallis test).

In a secondary analysis, we defined giant aneurysms as those with a *z*-score ≥10, in contrast to the traditional definition

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Table 4 Vascular Testing in KD and Control Populations

	KD (n = 203)	Control (n = 50)	p Value
Endo-PAT			
Endo-PAT index	n = 201	n = 50	
Mean ± SD	1.78 ± 0.46	1.70 ± 0.53	0.35
Median, range	1.74 (1.0–3.07)	1.55 (1.0–3.51)	0.13
Log Endo-PAT index	0.54 ± 0.26	0.49 ± 0.29	0.23
Reported pain level*			0.82
0	48 (24%)	12 (24%)	
1	71 (35%)	17 (34%)	
2	60 (30%)	16 (32%)	
3	21 (10%)	4 (8%)	
4	1 (<1%)	1 (2%)	
5	1 (<1%)	0 (0)	
Carotid artery ultrasound	203 (100%)	50 (100%)	—
Right carotid artery			
CCA IMT, mm†	0.428 ± 0.024	0.432 ± 0.029	0.35
CCA peak velocity, cm/s (n = 201, n = 48)	124 ± 24	118 ± 20	0.07
CCA elastic modulus, mm Hg (n = 201, n = 50)	277 ± 93	303 ± 98	0.09
ICA peak velocity, cm/s (n = 202, n = 49)	94 ± 21	90 ± 28	0.45
ICA end-diastolic velocity, cm/s (n = 202, n = 50)	33 ± 7	34 ± 9	0.39
ICA pulsatility index (n = 200, n = 49)	1.26 ± 0.36	1.13 ± 0.28	0.006
Left carotid artery			
CCA IMT, mm	0.438 ± 0.034	0.434 ± 0.028	0.42
CCA peak velocity, cm/s (n = 200, n = 48)	127 ± 23	120 ± 20	0.04
CCA elastic modulus, mm Hg (n = 201, n = 50)	282 ± 100	295 ± 89	0.34
ICA peak velocity, cm/s (n = 201, n = 50)	97 ± 23	91 ± 22	0.11
ICA end-diastolic velocity, cm/s (n = 201, n = 50)	35 ± 9	35 ± 9	0.93
ICA pulsatility index (n = 201, n = 50)	1.23 ± 0.33	1.14 ± 0.27	0.05

Values are mean ± SD, median (range), or n (%). *Wong-Baker Faces Pain Scale, ranging 0 to 5. †Average value of the IMT measurements in the anterior, posterior and lateral planes.

CCA = common carotid artery; Endo-PAT = endothelial pulse amplitude testing; ICA = internal carotid artery; IMT = intima-media thickness; KD = Kawasaki disease.

of ≥8 mm in maximum diameter used in the primary analysis. This lower threshold for the definition of giant aneurysms resulted in reclassification of 8 patients from group III to group IV. There were no longer any significant differences among the subgroups in measures of vascular health.

Our study entry criteria did not exclude smokers. Six of the 203 KD patients were smokers or admitted to smoking, whereas 3 of 50 control subjects reported to be smokers (3% vs. 6% respectively, p = 0.39). In a secondary analysis that excluded smokers, study inferences were unchanged.

Discussion

American Heart Association guidelines suggest that the long-term management of patients with KD be tailored to the degree of CA involvement (5). These recommendations, in contrast to Japanese guidelines (28), include lifetime follow-up for cardiovascular risk assessment and counseling every 3 to 5 years for KD patients who never had CA enlargement or had only transient CA ectasia. However, the risk of long-term adverse effects of KD on the coronary and peripheral vasculature among those who never had CA abnormalities is controversial. Some studies in this subgroup have shown preclinical abnormalities in endothelial function, IMT, arterial stiffness, and myocardial reserve (10,12,13,29–32), whereas others have not (33,34). Delineation of vascular sequelae is important because clinical or subclinical inflammation of the coronary and systemic arteries may form the substrate for longer term functional and structural abnormalities and increase the risk of premature atherosclerosis (7,35,36). In adults, peripheral vascular abnormalities are associated with CA health, but uncertainty about peripheral vascular abnormalities among KD patients with always normal CAs fuels the ongoing debate about their need for serial long-term cardiac follow-up (37,38).

In the current study, comprising the largest North American series of KD patients with vascular function testing to date, peripheral vascular health was evaluated at a mean of >11 years after illness onset. We found that the pulsatility index, which has been shown to be independently associated with high-sensitivity CRP levels in patients with essential hypertension (39), was higher in our KD population than in the control group. Similarly, a recent paper by Maurice and Dahdah (40) reported abnormal ascending aortic mechanical properties in KD patients compared with controls when measured by wall strain. However, in our study, KD patients with a history of normal CAs by 6 to 8 weeks after disease onset did not differ from healthy control subjects with respect to endothelial function, carotid IMT, and carotid stiffness.

Table 5 Control Group and KD Patients by Worst Ever Coronary Artery Status

	Control Group (n = 50)	No CA Enlargement (Group I) (n = 136)	Ectasia ($z \geq 2$, <3) (Group II) (n = 20)	Ectasia ($z \geq 3$, Aneurysm <8 mm) (Group II) (n = 40)	Giant Aneurysm (≥ 8 mm) (Group IV) (n = 7)	p Value
Endo-PAT						
Endo-PAT index	1.70 ± 0.53	1.79 ± 0.44	1.85 ± 0.46	1.72 ± 0.53	1.62 ± 0.35	0.55
Logarithm of Endo-PAT index	0.49 ± 0.29	0.56 ± 0.24	0.59 ± 0.24	0.49 ± 0.30	0.46 ± 0.20	0.35
Pain scale	1 (1, 2)	1 (1, 2)	1 (0, 2)	1 (0, 2)	1 (1, 2)	0.08
Carotid ultrasound						
Right CCA IMT,* mm	0.432 ± 0.03	0.429 ± 0.02	0.428 ± 0.03	0.424 ± 0.02	0.440 ± 0.04	0.41
Left CCA IMT,* mm	0.434 ± 0.03	0.439 ± 0.04	0.425 ± 0.02	0.434 ± 0.03	0.467 ± 0.05	0.05
Right CCA elastic modulus, mm Hg	303 ± 98	277 ± 97	294 ± 71	274 ± 95	242 ± 42	0.31
Left CCA elastic modulus, mm Hg	295 ± 89	280 ± 100	288 ± 86	283 ± 116	289 ± 73	0.92
Right CCA peak velocity, cm/s	118 ± 20	125 ± 23	129 ± 30	121 ± 23	116 ± 18	0.23
Left CCA peak velocity, cm/s	120 ± 20	127 ± 21	128 ± 21	127 ± 28	127 ± 25	0.42
Right ICA peak velocity, cm/s	90 ± 28	94 ± 20	91 ± 20	93 ± 24	89 ± 25	0.84
Left ICA peak velocity, cm/s	91 ± 22	97 ± 22	90 ± 22	101 ± 27	104 ± 16	0.20
Right ICA end-diastolic velocity, cm/s	34 ± 9	33 ± 7	34 ± 8	33 ± 9	30 ± 7	0.67
Left ICA end-diastolic velocity, cm/s	35 ± 9	35 ± 9	32 ± 9	35 ± 10	38 ± 6	0.53
Right ICA pulsatility index	1.13 ± 0.28	1.25 ± 0.35	1.23 ± 0.37	1.31 ± 0.42	1.26 ± 0.21	0.15
Left ICA pulsatility index	1.14 ± 0.27	1.21 ± 0.33	1.27 ± 0.29	1.26 ± 0.33	1.21 ± 0.41	0.38
Blood work						
CRP, mg/dl	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.1)	0.1 (0.1, 0.3)	0.37

Values are mean ± SD or median (25th, 75th percentiles). *Average value of the IMT measurements in the anterior, posterior and lateral planes.
CA = coronary artery; CCA = common carotid artery; ICA = internal carotid artery.

Our finding of normal peripheral vascular health among KD patients without CA abnormalities differs from findings of some other authors (13,29,32), but is consistent with those of other smaller studies in North America (12,33). Potential reasons for the differences in study results in this subgroup of KD patients include potential publication bias in the earlier reports (i.e., positive results are more likely to be published), differences in peripheral vascular health related to race and ethnicity, and differences in the modalities used to assess vascular health.

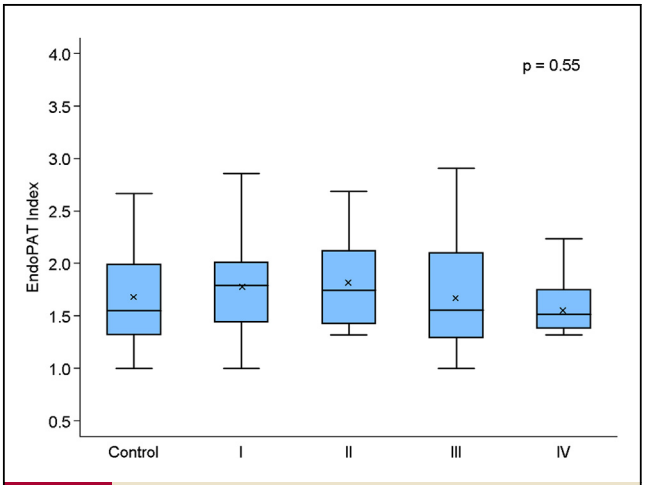

Figure 1 Boxplots of the Endothelial Pulse Amplitude Testing Index in the Kawasaki Disease Patient Groups and the Control Group

The x indicates the subgroup mean. The comparisons were made by 1-way analysis of variance. EndoPAT = Endothelial Pulse Amplitude Testing.

Our study had limited power to compare vascular health between control subjects and those with either regressed CA aneurysms or with concurrent CA aneurysms at the time of vascular testing. Nonetheless, patients with a history of giant aneurysms had thicker LCCA IMT and a trend toward lower reactive hyperemia (Endo-PAT) index, reflecting worse endothelial health. Similarly, the 10 KD patients with CA abnormalities at the time of vascular testing had a trend toward higher LCCA IMT and increased serum CRP. The carotid arterial wall of patients with persistent CA aneurysms (8,13) has been reported to have a higher IMT and increased stiffness, although these findings have not been confirmed by others (10).

Endothelial dysfunction has also been reported in KD patients. Ikemoto et al. (10) demonstrated decreased brachial artery flow–mediated dilation in patients with persistent CA aneurysms. Two other studies on endothelial function in patients with KD reported similar results (12,29). CRP levels have been reported to be significantly higher in patients with persistent CA aneurysms than those seen in normal age-matched children or among patients with KD without aneurysms or with regressed aneurysms, suggesting that the presence of aneurysms is associated with persistent systemic inflammation years after disease onset (41).

In patients with CA aneurysms that have regressed to normal internal lumen diameter, histopathology shows fibrous intimal thickening (42,43). In this group, intravascular ultrasound studies have reported myointimal thickening in the

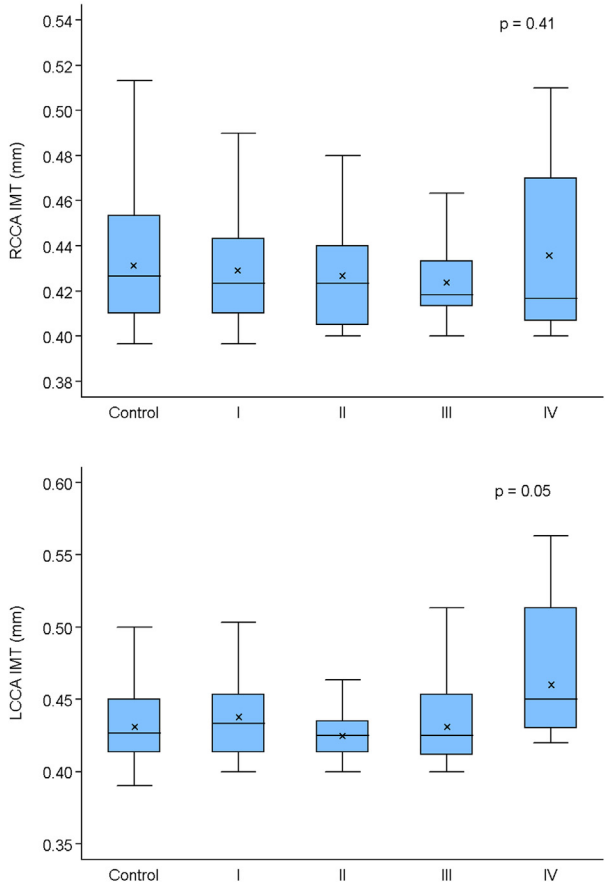

Figure 2 **Boxplots of the Intima-Media Thickness in Kawasaki Disease Patient Groups and the Control Group**

The **x** indicates the subgroup mean. The comparisons were made by 1-way analysis of variance. IMT = intima-media thickness; LCCA = left common carotid artery; RCCA = right common carotid artery.

CAs (44,45). These arteries demonstrate abnormal endothelial function with reduced vascular reactivity (11,46). In KD patients with persistent or regressed CA aneurysms, the proximal and peripheral arterial beds have also been reported to be stiffer compared with those in control subjects (13,47,48).

Study limitations. The strengths of the current study included its prospectively characterized KD population, use of CA *z*-scores, a large sample size for a rare disease, and the use of reliable modalities to assess vascular health. Our study should, however, be viewed in light of its limitations. We had a very small group of patients with giant aneurysms. Our population was drawn from a single site, and the predominantly non-Hispanic white study population precludes generalization of our findings to individuals of other races or ethnicities. Our control group consisted of North American youth, who may have had higher prevalence of cardiovascular risk factors than Asian control populations. A higher percentage of control subjects admitted to smoking in the 24 h before vascular testing. We did not check serum cotinine levels for objective ascertainment of the occurrence of smoking. However, analysis of the data omitting any patient who admitted to smoking did not change the study inferences. Finally, Orenstein et al. (49) recently published a post-mortem series of KD patients, demonstrating that the vasculopathic processes that characterize KD, including progression to luminal myofibroblastic proliferation, are distinct from those of atherosclerosis. Thus, it is possible that peripheral vascular health in KD patients might not reflect the health of the coronary arterial bed to the same extent as it does among individuals with atherosclerosis.

Conclusions

In summary, in contrast to some previous reports, this single-center study of late peripheral vascular function in a large population of North American adolescents with a history of KD demonstrated that patients whose maximum CA dimensions were either always normal or only mildly ectatic (*z*-score <3) had vascular health indexes that were similar to those of a healthy control group. Our study thus provides reassurance regarding peripheral vascular health in this population, supporting the contention of some investigators that these KD patients might not need lifetime specialized surveillance (37,50). The extent to which peripheral vascular function mirrors abnormalities in the CAs in patients with KD who never had aneurysms will become clearer as the earliest cohort of patients with KD enters middle age.

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