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Original article

Arterial stiffness in patients after Kawasaki disease without coronary artery involvement: Assessment by performing brachial ankle pulse wave velocity and cardio-ankle vascular index

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ABSTRACT

Background: It remains unclear whether systemic arterial beds other than the coronary arteries are truly healthy in patients without coronary artery lesions (CAL) after Kawasaki disease (KD). We tested the hypothesis that patients with KD without echocardiographic evidence of CAL during the acute phase of the disease have abnormal mechanical properties in systemic arteries later.

Methods and results: We studied 201 consecutive patients with KD (age 2–23 years, mean 10 ± 4 years; 109 male, 92 female) without CAL during the acute phase. Data were compared with those in 129 control subjects (age 2–25 years, mean 10 ± 4 years; 73 male, 56 female; control group). We examined arterial stiffness by using the brachial–ankle pulse wave velocity (baPWV) and the cardio-ankle vascular index (CAVI). The baPWV in the KD group was significantly higher than that in the control group (913 ± 121 cm/s vs. 886 ± 135 cm/s, $p = 0.04$). In contrast, there was no significant difference in CAVI (4.0 ± 1.0 vs. 4.2 ± 1.0, $p = 0.9$) between the two groups. Multivariate analysis indicated a highly significant difference in baPWV (higher baPWV in patients with KD than in controls, $p = 0.004$), after controlling for age, gender, body height and weight, and systolic and diastolic blood pressure, but no difference in CAVI between the groups.

Conclusion: Years after KD occurs in patients without apparent CAL during the acute phase, there is a small but significant change in systemic arterial properties, characterized by increased wall stiffness. The clinical importance of these findings must be clarified by performing long-term follow-up studies.

Introduction

Kawasaki disease (KD) [1,2] is the most commonly acquired cardiovascular disease in developed countries and has serious complications such as coronary vasculitis [3–5]. It has been reported that KD causes structural and functional abnormalities in systemic arterial beds, in addition to the coronary arteries, that can last for years after the resolution of the acute illness [6–9]. This is particularly true in patients who developed coronary artery lesions (CAL) during the acute phase [3,10,11].

However, the majority of patients with KD do not exhibit CAL, and information about the condition of systemic arterial beds in these patients is limited. Since the location and severity of KD-induced vasculitis are not uniform [3,10], KD might affect systemic arterial beds even in the absence of coronary artery abnormalities. In the present study, we tested the hypothesis that patients with KD but no echocardiographic evidence of CAL during the acute phase have abnormal systemic artery mechanical properties later. Therefore, we examined arterial stiffness in a large number of patients with a history of KD without CAL by using the measures of brachial–ankle pulse wave velocity (baPWV) [12] and the cardio-ankle vascular index (CAVI) [13–15].

Methods

Patients

We studied 201 consecutive patients with KD (age 2–26 years, mean 10 ± 4 years; 109 male, 92 female) who had developed either transient or no coronary artery dilation during the acute phase, based

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on transthoracic echocardiographic examination. These patients visited outpatient clinics at Saitama Medical University for periodic check-ups. Data were compared with those in 129 patients (age 2–25 years, mean 10 ± 4 years; 73 male, 56 female) who were considered to have normal systemic arteries (control group). The control subjects consisted of children who were referred to our clinics for suspected heart murmurs or abnormal electrocardiographic findings (i.e. incomplete right bundle branch block, grade I atrioventricular block), but turned out to be normal ($n = 95$). Patients with paroxysmal atrial or ventricular contractions ($n = 8$) or congenital heart disease with a trivial hemodynamic abnormality (i.e. a small ventricular or atrial septal defect, $n = 26$) were also included in the control group. The study was approved by the Institutional Review Board on Clinical Investigation at Saitama Medical University (No. 11-151, International Medical Center, Saitama Medical University).

Measurements

The baPWV was measured by using a volume-plethysmographic apparatus (Form/ABI; Colin Co., Ltd., Komaki, Aichi, Japan) as reported previously [16]. Briefly, the patient was examined in the supine position, sphygmomanometer cuffs were wrapped on both brachia and ankles, electrocardiogram electrodes were placed on both wrists, and a microphone was placed on the left edge of the sternum. The cuffs inflated and deflated automatically, and pulse wave contours in the four extremities were recorded simultaneously. The pulse transit time between the brachial and ankle regions was computed from these pulse volume recordings. The baPWV was determined from the pulse transit time and the distance between both segments.

The CAVI was measured with a VaSera VS-1000H (Fukuda Denshi Co., Ltd., Tokyo, Japan) by the methods described previously [14]. Specifically, the CAVI is determined by using the following procedure, based on the heart–ankle PWV (haPWV): haPWV is equal to the vascular length (L) from the aortic valve to the ankle divided by the propagation time (T) of the pulse wave. This propagation time (T) is determined by adding tb (the time difference between the 2nd heart sound and the initial pulse wave rise of the brachial artery) and tba (the time difference between the initial pulse wave rise of the brachial artery and that of the ankle artery). Finally, the haPWV is determined by using the following equation: haPWV = $L/(\mathrm{tb} + \mathrm{tba}) = L/T$. The CAVI is calculated by simultaneously inserting the measured blood pressure into the following equation:

$$\mathrm{CAVI} = a\left\{\left(\frac{2\rho}{\Delta P}\right) \times \ln\left(\frac{\mathrm{Ps}}{\mathrm{Pd}}\right) \times \mathrm{haPWV}^2\right\} + b \quad (1)$$

where Ps, systolic blood pressure; Pd, diastolic blood pressure; ΔP, Ps − Pd; haPWV, heart–ankle pulse wave velocity; ρ, blood density; a and b, constants.

The CAVI is finally approximated to the heart-femoral PWV by using the constants a and b so that it can be compared to conventional PWV. Thus, the CAVI reflects central arterial stiffness better than baPWV.

Vessel length was automatically estimated from the patient's height using a built-in algorithm based on the linear relationship between the two variables [14,16]. This algorithm is not necessarily validated for small children, especially those whose body length is <120 cm. Nonetheless, we applied the same algorithm for all subjects including small children, based on our preliminary study regarding the relationship between arterial length and body height. Using data obtained during cardiac catheterization, which provided a direct measurement of aortic length from the aortic root to the iliac artery, we found a strong linear correlation between arterial length and body length ($R = 0.95$) over a wide range of body lengths including those of small children (40–177 cm, $n = 60$).

Measurements were repeated until pressure wave signals of a good quality acceptable for analysis were obtained. In other words, if the pressure signals were of good quality, the measurements were performed just one time in each patient, which was the case in most of the present patients. Special care was taken for small children by asking the patients' parents to be in the examination room together throughout the measurements to calm the children. For the same purpose, we often let the children watch some cartoon videos during the measurements.

Statistical analyses

All values were expressed as mean ± SD. The significance of differences in the mean values between the groups was assessed by using the unpaired t-test. The differences in baPWV and CAVI between the groups were further tested after controlling for age, body mass index (BMI), sex, heart rate, and systolic and diastolic blood pressure by using a multivariate regression model. A probability value of $p < 0.05$ was considered to indicate statistical significance. All statistical analyses were performed by using JMP version 7.0 (SAS Institute, Inc., Cary, NC, USA).

Results

Patient characteristics for each group are listed in Table 1. The interval between the onset of KD to the time of this study was 7.0 ± 3.9 years, ranging from 6 months to 20 years. There were no significant differences in the data between the groups. As summarized in Table 2, baPWV in the KD group was slightly but significantly higher than that in the control group. In contrast, there was no significant difference in CAVI between the groups. Each group included 2 hypertensive and two obese children (0.99% vs. 1.6% for hypertension, $p = 0.65$, and 2.0% vs. 3.1% for obesity, $p = 0.49$), and the results were similar when these subjects were excluded from the analysis. As baPWV and CAVI are both influenced by blood pressure levels, and because arterial stiffness can be affected by several factors, including age, sex, heart rate, and BMI, we additionally

Table 1
Patient characteristics.

	Kawasaki disease ($N = 201$)		Control ($N = 129$)		p-Value
	Mean ± SD	Range	Mean ± SD	Range	
Age (years)	10 ± 4.1	2.3–26	10 ± 4.7	2.5–25	0.58
Female (%)	40		37		0.73
Height (cm)	134 ± 21	88–176	135 ± 23	92–183	0.61
Body weight (kg)	34 ± 14	12–69	35 ± 16	13–87	0.48
Body mass index (kg/m^2)	17.6 ± 2.6	12–26	17.7 ± 3.6	12–33	0.65
Systolic blood pressure (mmHg)	105 ± 11	84–145	108 ± 11	82–137	0.98
Diastolic blood pressure (mmHg)	61 ± 8	38–91	63 ± 7.6	44–83	0.95
Heart rate (bpm)	75 ± 12	51–113	73 ± 12	45–107	0.46
Interval from the onset of Kawasaki disease (years)	7.0 ± 3.9	0.5–20			

Table 2
Comparison of baPWV and CAVI.

	Kawasaki disease ($N=201$)		Control ($N=129$)		p-Value
	Mean ± SD	Range	Mean ± SD	Range	
baPWV	913 ± 121	665–1268	886 ± 135	530–1282	0.04
CAVI	4.0 ± 1.0	2.2–8.8	4.2 ± 1.0	1.7–7.4	0.90

baPWV, brachial–ankle pulse wave velocity; CAVI, cardio-ankle vascular index.

Table 3
Effect of factors on the brachial–ankle pulse wave velocity.

Independent predictors	Coefficient	R^2	p-Value
SBP (per mmHg)	6.70	0.228	<0.001
Age (per year)	4.00	0.325	0.035
Group (1 vs. 2)[a]	−32.0	0.288	0.009
Heart rate (bpm)			0.299
BMI			0.603
Sex (male vs. female)			0.974

SBP, systolic blood pressure; BMI, body mass index.
[a] Group was assigned as a categorical variable, with 1 for Kawasaki disease without coronary artery lesions and 2 for the control group.

compared baPWV and CAVI between the groups after controlling for these factors in a multivariate analysis. The results indicated a highly significant difference in baPWV (higher baPWV in patients with KD than in controls, $p = 0.009$; Table 3). There was no significant difference in CAVI between the groups even after controlling for these factors.

Discussion

Because CAL in KD is an important complication that significantly influences the prognosis, the pathophysiology of coronary arteries in this disease has been studied extensively [17–20]. Furthermore, consistent with the fact that KD presents as a systemic vasculitis that can involve any type of vessel, structural and functional abnormalities in pulmonary arteries as well as systemic arteries other than coronary arteries have also been reported in both acute and chronic phases of KD [10]. However, such studies have been carried out primarily in patients with coronary artery involvement during the acute phase, and data regarding the state of systemic arteries in the chronic stage of disease in patients with KD without CAL are limited. In addition, the results of these studies are conflicting, as summarized in Table 4. Dhillon et al. [21] were the first to present data suggesting the possibility of long-lasting abnormalities in systemic arterial function in patients with KD without a history of coronary artery involvement. They studied endothelial-dependent and -independent dilation in the brachial arteries of 20 patients after KD. Of these, three patients who had CAL during the acute illness were included. The authors demonstrated that flow-mediated arterial dilation (FMD), which indicates endothelium-dependent dilation, but not the response to glyceryl trinitrate (GTN), an endothelium-independent dilator, was reduced in patients with KD, even in those without detectable early coronary artery involvement. These results, however, were not reproduced in a subsequent study by McCrindle [22], who compared 52 patients with KD with varying levels of coronary artery involvement to 60 healthy control subjects. Of these, 30 patients with KD had no history of coronary artery involvement during the acute stage. The author found no significant differences in FMD or GTN response in the brachial artery between KD and control subjects, independent of a history of coronary artery involvement. Ikemoto et al. [23] also reported that FMD of the brachial artery in 31 patients with KD without CAL was comparable to that in 20 healthy controls. Other studies have assessed arterial stiffness in patients with KD without CAL, but the results were also inconsistent. Cheung et al. [24] assessed the stiffness of brachioradial arteries of 29 patients with KD without CAL by measuring the local PWV and demonstrated that the PWV of these patients was comparable to that in 37 patients with KD and CAL and was significantly higher than that in 36 age-matched controls. On the other hand, these results were not observed by Ikemoto et al., who reported no significant difference in the brachial artery stiffness index between patients with KD and controls [23].

Therefore, results regarding the state of systemic arterial beds after KD in patients without CAL are so far inconsistent. This might be largely due to the small number of patients in each study. In addition, abnormalities in the systemic vascular beds in patients with KD, if present, may be too subtle to yield consistency among studies with few subjects. In fact, there was significant overlap in the data even in the studies of Dhillon and Cheung that demonstrated significant differences in FMD and PWV between patients with KD and controls [21,24]. The fact that our results were obtained from a large number of study subjects and demonstrated a small but significant increase in baPWV in patients with KD is consistent with the above-mentioned results. Therefore, taken together, it appears safe to say that systemic arteries are not necessarily normal in patients with KD, even in those without detectable coronary artery involvement. Results of pathological studies [8,9,25–28] demonstrating intimal thickening with fibrous scar formation and smooth muscle proliferation in systemic arteries of children who have had KD even years after resolution of acute illness fit with our data of increased baPWV in the later phase of KD.

Of note, in this study we observed a significant difference in baPWV between patients with KD and the control group but not in CAVI. Both baPWV and CAVI are indices of arterial stiffness, but CAVI reflects stiffness of the whole arterial system from the aortic root to the lower extremities and baPWV reflects the arterial

Table 4
Summary of previous studies investigating properties of systemic arteries in Kawasaki disease patients without coronary artery involvement.

Authors	Number of KD patients without CAL	Number of controls	Patients' age (years)	Follow-up period (years)	Key findings
Dhillon et al. [21]	17	20	13.0[a]	11.3[a]	FMD ↓ GTN →
McCrindle [22]	30	60	15.5 ± 2.3[b]	11.2 ± 3.7[b]	FMD → GTN →
Ikemoto et al. [23]	31	20	13.1 ± 2.6	11.6 ± 1.6	FMD → Stiffness →
Cheung et al. [24]	29	36	8.9 ± 3.2	6.2 ± 2.4	bPWV ↑

KD, Kawasaki disease; CAL, coronary artery lesions; FMD, flow-mediated dilation; GTN, glyceryl trinitrate; bPWV, brachioradial pulse wave velocity. (↓) Reduced, (↑) increased, and (→) no change.
[a] Average data including 3 patients with coronary artery involvement.
[b] Average data including 22 patients with coronary artery involvement.

stiffness from the abdominal aorta to the lower extremities (Eq. (1)). Thus, a disparity in changes between baPWV and CAVI suggests that peripheral arteries are the site of the primary lesions that last years after the acute phase of KD, even in patients without coronary artery involvement. This is consistent with the fact that the vasculitis associated with KD is most evident in small- and medium-sized arteries. The results also suggest that measuring both baPWV and CAVI might be useful to determine the location of arterial stiffness.

Clinical implications

There is ongoing controversy about whether and/or how physicians should follow patients with KD without evidence of CAL [29]. Establishing a follow-up protocol (including the discontinuation of follow-up) is as important in these patients as in patients with cardiac complications, because patients without CAL constitute the majority of patients with a history of this disease. Arterial stiffness directly influences left ventricular afterload [30] and coronary perfusion [31], and it also appears to be approximately parallel to the extent of atherosclerosis in adults [32]. Arterial stiffening per se may be sufficient to cause endothelial dysfunction [32]. Additionally, in longitudinal studies of several diseases and conditions, arterial stiffness was shown to be an independent predictor of cardiovascular morbidity and mortality [33]. Thus, the results of the present study support the need for long-term follow-up of patients with KD, even those without evidence of CAL. As part of the follow-up, noninvasive assessments of arterial stiffness and endothelial function should also be incorporated.

Limitations

Our control group included patients who might not have truly normal arteries (particularly those with atrial and ventricular septal defects). However, the PWV values in the present control group were similar to those reported in a previous study by Niboshi et al. [34]. In addition, even if the arteries were not completely normal in the present controls, this strengthens rather than weakens our key finding of increased PWV in patients with KD. Although a previous study indicated excellent reproducibility of PWV measurements even in small children [35], we did not test data reproducibility in the present study. Instead, we tried to secure the accuracy of data by repeating measurements until we obtained good quality signals acceptable for the analysis. This point needs to be acknowledged as a study limitation. Vessel lengths used for the calculation of PWV and CAVI were not directly measured but estimated from the patient's height based on the uniform relationship between the vessel length and body height independent of the patient's age. This could be a source of errors in calculated PWV and CAVI. However, age distribution was similar between the two groups; thus, potential errors due to applying the same algorithm to all study subjects should have been equally introduced for each group. Also, as already mentioned, our control data were similar to those of the previous study by Niboshi et al. [34]. Therefore, we believe the validity of the present results. Lastly, the present study was cross-sectional; thus, serial assessment of arterial stiffness should be performed to further clarify the pathological importance of increased arterial stiffness in patients with KD without coronary artery involvement.

Conclusions

We observed a small but significant change in systemic arteries, characterized by increased wall stiffness, years after the acute phase of KD in patients without apparent CAL during the acute phase of the disease. The clinical importance of these findings must be clarified by long-term follow-up studies.

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Conflict of interest

The authors declare that there is no conflict of interest.

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