Journal of Cardiology 66 (2015) 130–134

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

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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ARTICLE INFO

Article history:
Received 4 February 2014
Received in revised form 10 September 2014
Accepted 1 October 2014
Available online 7 November 2014

Keywords:
Kawasaki disease
Arterial stiffness
Pulse wave velocity
Cardio-ankle vascular index

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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http://dx.doi.org/10.1016/j.jjcc.2014.10.003
0914-5087/

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			