

# Arterial stiffness late after Kawasaki disease in children: Assessment by performing brachial–ankle pulse wave velocity

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## Abstract

**Background:** Whether low-risk Kawasaki disease (KD) patients are at increased risk of cardiovascular disease later in life remains controversial. The purpose of this study is to examine the arterial stiffness and exercise performance of KD patients in chronic stage.

**Methods:** This study included 158 subjects. They were divided into three groups: 37 KD patients with regressed coronary artery lesions (CALs) (M/F 23/14, 13.6 ± 6.5 years) (group I), 43 KD patients without CALs (M/F 26/17, 13.9 ± 6.2 years) (group II), and 78 age- and gender-matched normal controls (M/F 44/34, 13.2 ± 6.9 years) (group III). They all underwent brachial–ankle pulse wave velocity (baPWV), an exercise test, and blood sampling to measure the levels of high-sensitivity C-reactive protein (hs-CRP), triglycerides (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and total cholesterol (TC). The differences among the groups were compared.

**Results:** There were significant differences among the three groups in terms of right and left baPWV ( $p < 0.01$  respectively), HDL level ( $p < 0.05$ ), TC/HDL ratio ( $p < 0.05$ ), and oxygen consumption ( $\text{VO}_2$ ) peak ( $p < 0.05$ ). Moreover, group I subjects had significantly higher right and left baPWV ( $p < 0.05$  respectively), lower HDL level ( $p < 0.05$ ), and lower  $\text{VO}_2$  peak ( $p < 0.05$ ) than group II subjects. Furthermore, baPWV was significantly correlated with TG level ( $r = 0.326, p < 0.05$ ), TC/HDL ratio ( $r = 0.483, p < 0.01$ ), LDL level ( $r = 0.386, p < 0.01$ ), and  $\text{VO}_2$  peak ( $r = -0.385, p < 0.05$ ) in group I subjects. Only the TC/HDL ratio was found to be a significant correlating factor for an increase of baPWV (beta = 0.68,  $p < 0.05$ ) in KD patients after multiple linear regression.

**Conclusion:** Our results suggest that arterial stiffness is present late after KD and may adversely affect exercise performance, especially in patients with regressed CALs. Regular measurement of baPWV may be indicated in the long-term follow-up of KD patients.

**Keywords:** Brachial–ankle pulse wave velocity; Echocardiography; Exercise test; High-sensitivity C-reactive protein; Kawasaki disease; Lipid profile

## 1. INTRODUCTION

Kawasaki disease (KD), an acute systemic vasculitis with a predilection for the Asian race, occurs mainly in infants and children under 5 years of age.<sup>1</sup> It is frequently complicated by the

development of coronary artery lesions (CALs) which occur in approximately 15%–25% of untreated KD children and in about 5% of those after intravenous immunoglobulin (IVIG) therapy.<sup>1,2</sup> KD is recognized as the leading cause of acquired heart disease in children.<sup>1,2</sup> The etiology of KD remains unknown and may be attributed to the combined effects of infection, immune response, and genetic susceptibility.<sup>1,2</sup> The annual incidence of KD in Taiwan is estimated to be 45.8–82.8/100,000 children younger than 5 years old, the third highest in the world after Japan and Korea.<sup>3</sup>

The previous studies revealed that KD patients in chronic stage had ongoing low grade inflammation, lipid disorder, and vascular endothelial dysfunction, which may contribute to the early onset of atherosclerosis.<sup>4–18</sup> Whether low-risk KD patients are at increased risk of cardiovascular disease remains controversial.<sup>19</sup> This makes the measurement of subclinical vascular changes in KD patients an important issue. Vascular health in KD can be assessed using carotid intima-media thickness (CIMT),<sup>4,6,10,11,16,18</sup> flow-mediated dilatation (FMD),<sup>12–15</sup> brachial–ankle pulse wave velocity (baPWV),<sup>5,10,17</sup> and some

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biomarkers such as cell adhesion molecule.<sup>10</sup> CIMT is the most widely studied method in KD. The studies including subjects of Asian ethnicity (including Japanese) reported increased CIMT even in patients who have always had normal coronary arteries.<sup>4,6,11,16,18</sup> In contrast, no CIMT differences were found between KD patients and healthy controls in a large British study.<sup>10</sup> Two recent studies<sup>16,18</sup> showed that CIMT in patients without CALs is indistinguishable from normal controls at a more advanced age, whereas an increased CIMT is observed at any age in patients with CALs. FMD measures the percentage increase in the size of the brachial artery using ultrasound before and after suprasystolic occlusion and is a noninvasive measure of endothelial function. Most studies in KD patients show a decrease in FMD compared with the controls.<sup>12-15</sup> Significant changes in FMD are found in KD patients without abnormal CIMT.<sup>13</sup> This is consistent with the previous findings in atherosclerosis in which functional vascular changes precede structural abnormalities.<sup>20</sup> Measurement of baPWV is a non-invasive method representative of arterial stiffness.<sup>21</sup> Studies of baPWV in KD are limited.<sup>5,10,17</sup> Some studies<sup>5,17</sup> demonstrated an increase in baPWV following KD, but a report from England<sup>10</sup> did not show any differences in PWV between KD patients and normal controls. These previous studies of vascular changes in patients late after KD highlight the spectrum of associated vascular abnormalities. KD patients with chronic CALs have increased CIMT, decreased FMD, and increased baPWV compared with the controls, although data are inconsistent. KD patients without CALs, in general, have no significant different CIMT compared with the controls, but some data indicate endothelial dysfunction and increased arterial stiffness.<sup>5-7,10-15,17</sup>

A previous study by Tuan et al showed that KD patients with/without CALs in chronic stage might still have compromised coronary perfusion during exercise, which was related to the Z score of the coronary artery.<sup>22</sup> The long-term effect of these subclinical vascular changes on cardiovascular function is still unclear and merits further evaluation. The purpose of this study is to examine the arterial stiffness using baPWV and exercise performance of KD patients in chronic stage.

## 2. METHODS

### 2.1. Subjects

This study consisted of 80 KD patients aged more than 5 years in chronic stage at our hospital. Medical records of these KD patients were reviewed for age, sex, KD onset, and coronary complications. KD patients underwent two-dimensional echocardiography at the time of diagnosis and again at weeks 2, 4, 8, and 12 after treatment, the sixth month, and annually in follow-up. They were divided into two groups according to CALs in acute stage within 2 weeks of illness. CALs is defined as Z score  $\geq 2.0$ .<sup>23,24</sup> Regressed CALs is defined as Z score  $< 2.0$  beyond 1 year. Group I consisted of 37 KD patients with regressed CALs who had CALs in acute stage. Group II consisted of 43 KD patients without CALs. We recruited 78 age- and sex-matched normal controls (Group III) who had a functional heart murmur or chest pain without organic lesion diagnosed at our OPD. All subjects underwent echocardiography, baPWV, treadmill testing, blood sampling for measurement of high-sensitivity C-reactive protein (hs-CRP), triglycerides (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and total cholesterol (TC). The study was approved by the Institutional Review Board of Kaohsiung Veterans General Hospital (IRB number: VGHKS16-CT8-23). All written informed consents were obtained from the adult subjects or guardians on behalf of the children involved in this study.

### 2.2. Measurement of hs-CRP and lipid profile

Three milliliters of heparinized venous blood was taken from each subject in the fasting state for at least 8 hours, with the study participants in a supine position for at least 20 minutes. Blood samples were centrifuged immediately after collection, and plasma was separated for measurement of hs-CRP and lipid profile including TG, HDL, LDL, and TC.

### 2.3. BaPWV (brachial-ankle pulse wave velocity)

BaPWV was measured with an automatic apparatus (VP-1000 plus; OMRON Health Care Co, Kyoto, Japan). Participants rested for at least 15 minutes to stabilize their heart rate and were then examined in a supine position with a pneumatic cuff connected to a plethysmographic sensor wrapped on both brachia and ankles. The cuffs inflated and deflated automatically and pulse waveforms in the four extremities were recorded concurrently. At the same time, an oscillometric pressure sensor used to measure blood pressure was placed on both upper arms and ankles, with electrocardiographic recording continuing during the procedure. The average of three readings was taken. The mean of the right and left baPWV values was used for the analysis. All measurements were performed by the same examiner.

### 2.4. Exercise test

We used symptom-limited treadmill exercise test to measure the patients' exercise capacity. This testing system incorporated a treadmill, a flow module, a gas analyzer, and an electrocardiographic monitor (Metamax 3B, Cortex Biophysik GmbH Co., Germany). Subjects underwent the exercise test according to the Bruce protocol suggested by the American College of Sports Medicine. We terminated the test when the subjects demonstrated subjective unbearable symptoms.<sup>25</sup> The oxygen consumption ( $\text{VO}_2$ ) was measured by the breath-by-breath method during the testing.

### 2.5. Statistical analysis

Continuous variables are expressed as means with standard deviation. Categorical variables are presented as absolute numbers and percentages. Comparison of continuous variables between two groups was carried out using the two-tailed unpaired *t*-test. To compare the differences in variables among the three groups, one-way analysis of variance was performed. Post-hoc analysis with Bonferroni correction was then performed to compare the differences between two groups. Correlation analysis was carried out using the Pearson correlation method. Stepwise multiple linear regression was used to identify significant correlating factors for an increase of baPWV. A *p* value  $< 0.05$  was considered statistically significant.

## 3. RESULTS

There were 37 KD children with regressed CALs (M/F 23/14,  $13.6 \pm 6.5$  years) in group I, 43 KD children without CALs (M/F 26/17,  $13.9 \pm 6.2$  years) in group II, and 78 normal controls (M/F 44/34,  $13.2 \pm 6.9$  years) in group III. Baseline characteristics of three groups are shown in Table 1. There were no significant differences in age and sex among the three groups. The interval from KD onset between group I and group II was also not statistically different ( $9.9 \pm 4.3$  vs  $9.7 \pm 4.9$  years, *p*  $> 0.05$ ).

### 3.1. Comparison of baPWV, laboratory data, and $\text{VO}_2$ peak among the three groups

As shown in Table 2, there were significant differences among the three groups in terms of right and left baPWV (*p*  $< 0.01$  respectively), HDL level (*p*  $< 0.05$ ), TC/HDL ratio (*p*  $< 0.05$ ),

**Table 1****Demographic data in the three groups**

	Group I (n = 37)	Group II (n = 43)	Group III (n = 78)	p
Age (y)	13.6 ± 6.5	13.9 ± 6.2	13.2 ± 6.9	NS
Sex (NS)				
Female	14 (38%)	17 (40%)	34 (44%)	
Male	23 (62%)	26 (60%)	44 (56%)	
Interval from KD onset (years)	9.9 ± 4.3	9.7 ± 4.9		NS

KD = Kawasaki disease; NS = nonsignificant.

and oxygen consumption ( $VO_2$ ) peak ( $p < 0.05$ ). There were no significant differences in the three groups in terms of hs-CRP level, TG level, LDL level, and TC level. Compared with group III control subjects, group I subjects had significantly higher right and left baPWV ( $p < 0.01$ , respectively), lower HDL level ( $p < 0.05$ ), higher TC/HDL ratio ( $p < 0.05$ ), and lower  $VO_2$  peak ( $p < 0.05$ ). Group II subjects had significantly higher right and left baPWV ( $p < 0.05$ , respectively) and higher TC/HDL ratio ( $p < 0.05$ ) than group III control subjects. Moreover, group I subjects had significantly higher right and left baPWV ( $p < 0.05$ , respectively), lower HDL level ( $p < 0.05$ ), and lower  $VO_2$  peak ( $p < 0.05$ ) than group II subjects. The mean baPWVs of the three groups were  $932.7 \pm 135.7$ ,  $873.5 \pm 150.6$ ,  $798.5 \pm 166.3$  cm/s, separately. Fig. 1 shows the significant differences of baPWV in the three groups.

### 3.2. Correlation of baPWV and laboratory data in groups I and II

In group I subjects, baPWV was significantly correlated with TG level ( $r = 0.326$ ,  $p < 0.05$ ), TC/HDL ratio ( $r = 0.483$ ,  $p < 0.01$ ), LDL level ( $r = 0.386$ ,  $p < 0.01$ ), and  $VO_2$  peak ( $r = -0.385$ ,  $p < 0.05$ ). There was no significant correlation between baPWV and other laboratory data in KD patients with CALS in terms of hs-CRP level, HDL level, and TC level (Table 3). In group II subjects, there was no significant correlation between baPWV and laboratory data in terms of hs-CRP level, TG level, HDL level, TC/HDL ratio, LDL level, TC level, and  $VO_2$  peak (Table 4).

### 3.3. Correlating factors for increased baPWV in KD patients (group I + group II) after stepwise multiple linear regression

Stepwise multiple linear regression analysis of 80 KD patients was used to identify correlating factors for increased baPWV. The variables included age, gender, interval from the onset of KD, hs-CRP level, TG level, HDL level, TC/HDL ratio, LDL

level, and TC level. Only the TC/HDL ratio was found to be statistically significant ( $\beta = 0.68$ ,  $p < 0.05$ ) (Table 5).

## 4. DISCUSSION

Our results demonstrated that KD patients have an increased baPWV compared with normal controls many years after acute KD. Arterial stiffness reflected by baPWV was more severe in KD patients with regressed CALS. Compared with normal controls and KD patients without CALS, KD patients with regressed CALS had lower  $VO_2$  peak, which was significantly correlated with baPWV. This implies the arterial stiffness may adversely affect the cardiac function and exercise performance subclinically in KD patients, especially those with regressed CALS.

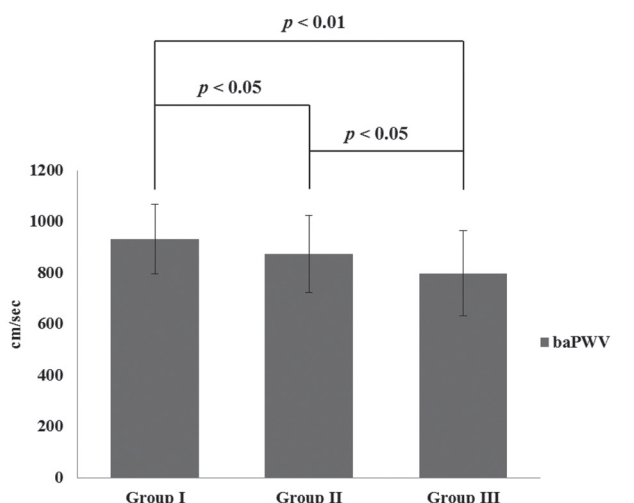
CALS develop in approximately 15%–25% of untreated KD children and in about 5% of those after IVIG therapy.<sup>1,2</sup> The effect of CALS on cardiovascular function in KD patients has been an important issue. Measurement of baPWV is a noninvasive method representative of arterial stiffness.<sup>21</sup> Cheung et al reported that KD patients with/without CALS in chronic stage ( $n = 66$ ) had higher baPWV than normal controls ( $n = 36$ ).<sup>5</sup> Lee et al demonstrated that KD patients with previous CALS ( $n = 25$ ) had higher baPWV than normal controls ( $n = 55$ ).<sup>26</sup> They emphasized the importance of baPWV in long-term follow-up of KD patients, especially those with no abnormality in echocardiography.<sup>26</sup> Cho et al's study revealed that higher PWV was higher in school aged KD children ( $n = 68$ ) than in normal controls ( $n = 30$ ). Compatible with these previous studies,<sup>5,17,26</sup> our series with a relatively large sample size (KD [ $n = 80$ ], normal controls [ $n = 78$ ]) further showed higher baPWV in KD patients with regressed CALS and without CALS compared with the normal controls. On the contrary, Shav et al reported there was no difference in PWV between KD patients ( $n = 120$ ) and normal controls ( $n = 51$ ), but they still found higher markers of endothelial injury in KD patients.<sup>10</sup> The mechanisms of KD on arterial stiffness may include replacement of vascular elastic tissue by fibrous scar in the chronic KD stage,<sup>27</sup> and endothelial dysfunction after KD.<sup>12</sup> A prospective longitudinal study using both baPWV and endothelial markers is recommended to investigate the endothelial dysfunction late after KD.

In this series, KD patients with regressed CALS had significantly lower HDL than normal controls. In the acute stage of KD, low HDL was an important finding in previous studies.<sup>28–31</sup> The effect of low HDL on KD is controversial. Both studies by Cabana et al and Salo et al suggested low HDL in the acute stage of KD is transient and not considered as a risk factor for atherosclerosis.<sup>30,31</sup> On the contrary, some studies, including ours, reported that low HDL cholesterol levels persist in patients

**Table 2****Comparison of baPWV, laboratory data, and  $VO_2$  peak among the three groups**

	Group I (n = 37)	Group II (n = 43)	Group III (n = 78)	p (ANOVA)	p		
					I vs II	I vs III	II vs III
RbaPWV (cm/s)	931.5 ± 134.0	884.7 ± 135.5	826.0 ± 101.8	<0.01	<0.05	<0.01	<0.05
LbaPWV (cm/s)	933.9 ± 137.4	862.4 ± 165.7	771.0 ± 230.7	<0.01	<0.05	<0.01	<0.05
hs-CRP (mg/dl)	0.12 ± 0.14	0.07 ± 0.12	0.08 ± 0.18	NS	NS	NS	NS
TG (mg/dl)	86.4 ± 49.0	74.6 ± 54.7	79.2 ± 42.6	NS	NS	NS	NS
HDL (mg/dl)	51.9 ± 9.3	60.4 ± 12.9	63.3 ± 13.6	<0.05	<0.05	<0.05	NS
TC/HDL	3.1 ± 0.7	2.9 ± 1.2	2.7 ± 0.7	<0.05	NS	<0.05	<0.05
LDL (mg/dl)	82.2 ± 23.0	86.6 ± 26.7	93.0 ± 30.0	NS	NS	NS	NS
TC (mg/dl)	157.3 ± 29.3	170.2 ± 31.5	165.7 ± 30.3	NS	NS	NS	NS
$VO_2$ peak (MET)	9.3 ± 1.6	10.5 ± 1.6	10.5 ± 1.8	<0.05	<0.05	<0.05	NS

ANOVA = one-way analysis of variance; hs-CRP = high-sensitivity C-reactive protein; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; LbaPWV = left brachial-ankle pulse wave velocity; MET = metabolic equivalent; NS = nonsignificant; RbaPWV = right brachial-ankle pulse wave velocity; TC = total cholesterol; TG = triglycerides;  $VO_2$  = oxygen consumption.



**Fig. 1.** Comparison of baPWV in the three groups. baPWV = brachial-ankle pulse wave velocity.

with CALs.<sup>5,29</sup> Severe inflammation in acute CALs may have an adverse effect on late lipid metabolism, including low HDL.<sup>29</sup> The relationship between an altered lipid profile and early atherosclerosis requires further studies.

In our patients with regressed CALs, baPWV was significantly correlated with TG level, TC/HDL ratio, LDL level, and VO<sub>2</sub> peak. Our results further showed the TC/HDL ratio is a significant correlating factor for increased baPWV in KD patients after multiple linear regression. This highlights the effect of lipid changes on arterial stiffness. The negative correlation of the

**Table 3**

**Correlation between baPWV and laboratory data in KD patients with regressed CALs (group I)**

	Correlation coefficient	p
hs-CRP	0.163	NS
TG	0.326	<0.05
HDL	-0.168	NS
TC/HDL	0.483	<0.01
LDL	0.386	<0.01
TC	0.192	S
VO <sub>2</sub> peak	-0.385	< 0.05

baPWV = brachial-ankle pulse wave velocity; hs-CRP = high-sensitivity C-reactive protein; HDL = high density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; NS = nonsignificant; TC = total cholesterol; TG = triglycerides; VO<sub>2</sub> = oxygen consumption.

**Table 4**

**Correlation between baPWV and laboratory data in KD patients without CALs (group II)**

	Correlation coefficient	p
Hs-CRP	0.009	NS
TG	0.224	NS
HDL	-0.026	NS
TC/HDL	0.289	NS
LDL	0.269	NS
TC	0.189	NS
VO <sub>2</sub> peak	-0.108	NS

baPWV = brachial-ankle pulse wave velocity; hs-CRP = high-sensitivity C-reactive protein; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; NS = nonsignificant; TC = total cholesterol; TG = triglycerides; VO<sub>2</sub> = oxygen consumption.

**Table 5**

**Correlating factors for increased baPWV in KD patients (group I + group II)**

	Multivariate beta	p
Age	0.26	NS
Sex	0.18	NS
Interval from KD onset	0.35	NS
Hs-CRP	0.42	NS
TG	0.32	NS
HDL	-0.49	NS
TC/HDL	0.68	<0.05
LDL	0.41	NS
TC	0.39	NS

baPWV = brachial-ankle pulse wave velocity; hs-CRP = high-sensitivity C-reactive protein; HDL = high-density lipoprotein cholesterol; KD = Kawasaki disease; LDL = low-density lipoprotein cholesterol; NS = non-significant; TC = total cholesterol; TG = triglycerides.

baPWV and VO<sub>2</sub> peak is also a very important finding, reflecting the adverse effect of arterial stiffness on the cardiac function and exercise function subclinically in KD patients, especially those with regressed CALs. Tuan et al reported KD patients with/without CALs in chronic stage might still have compromised coronary perfusion during exercise.<sup>22</sup> The correlation of the baPWV and VO<sub>2</sub> peak may partially explain their finding.<sup>22</sup> Regular measurement of baPWV is useful to evaluate the degree of early atherosclerosis and cardiac dysfunction in KD patients.

Some limitations in this study needs to be specified. This is a single-center investigation with limited number of patients and a cross-sectional nature. Patients with different shapes or sizes of coronary arterial lesions were not analyzed because persistent aneurysm was not included in this series. The markers of endothelial function were not measured. A multicenter study with a large cohort in a longitudinal manner is suggested.

In conclusion, our results suggest that arterial stiffness is present late after KD and may adversely affect exercise performance, especially in patients with regressed CALs. Regular measurement of baPWV may be indicated in the long-term follow-up of KD patients.

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