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Evaluation of Arterial Functions and Carotid Intima Media Thickness in Children During Mid-Term Follow-Up After Kawasaki Disease

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What is already known on this topic?

- *Kawasaki Disease (KD) is a multisystemic vasculitis that may lead to long-term cardiovascular sequelae.*

What this study adds on this topic?

- *This is the first study combining the ultrasonographic measurement of vascular functions and biomarkers indicating cardiovascular risk, in patients with previous KD.*
- *Impaired arterial functions may indicate increased risk for atherosclerotic cardiovascular disease (CVD) in children, following KD.*

ABSTRACT

Objective: Kawasaki disease (KD) is a multisystemic vasculitis of medium- and small-sized arteries. The involvement of the coronary arteries may lead to long-term cardiovascular sequelae. We studied the elasticity of the aorta and the common carotid artery (CCA), flow-mediated dilatation of the brachial artery, and carotid intima media thickness, as well biomarkers such as high-sensitivity C-reactive protein (hs-CRP) and elastin, as useful indicators of cardiovascular risk in patients, following KD.

Methods: The study group consisted of 26 patients with a history of KD, and 26 healthy children. Echocardiography, and carotid and brachial ultrasound studies were performed. Plasma hs-CRP and elastin levels were studied in both groups.

Results: The stiffness indices (SI) obtained from the aortic arch, abdominal aorta, and the CCA were increased in the patients, compared to the controls. Distensibility was decreased at the sinus of Valsalva, the sinotubular junction, the aortic arch, and the ascending aorta, compared to the control group. Flow-mediated dilatation (FMD) was lower in the patients than in the controls. The age of the patients had a negative correlation to distensibility of the aortic arch and abdominal aorta, and a positive correlation to the stiffness of the aortic arch. Follow-up duration correlated positively to stiffness of the aortic arch. Carotid intima-media thickness (CIMT), serum hs-CRP, and elastin levels did not differ between the groups.

Conclusion: Increased aortic and carotid stiffness and decreased aortic distensibility suggest impaired arterial functions following KD. Long-term follow-up and monitorization early in cardiovascular disease is needed.

Keywords: Arterial distensibility, arterial stiffness, cardiovascular risk, Kawasaki disease, long-term follow-up

INTRODUCTION

Kawasaki disease (KD) is a multisystemic vasculitis of medium- and small-sized arteries, especially the coronary arteries, that may cause long-term cardiovascular sequelae. The major concerns for pediatricians are coronary artery aneurysms and dilatation, which are found in 15% to 25% of untreated patients, which may be followed by myocardial ischemia/infarction, or sudden death as a consequence.[1,2] Treatment with high-dose intravenous immunoglobulin (IVIG) has decreased this risk from 25% down to 3-5%. However, KD is still the leading cause of acquired heart disease in children of industrialized countries.[3]

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Recent research has focused on endothelial damage and early onset of atherosclerosis in patients with KD. Angiography and autopsy studies have demonstrated that coronary sequelae may persist long after acute KD vasculitis, and lead to atherosclerotic changes resulting in late coronary events or sudden death in adults. Conventional echocardiography and coronary angiography demonstrate coronary aneurysms or stenoses, but are insufficient in the detection of early stages of atherosclerosis.[4]

Various non-invasive diagnostic methods have been used to evaluate the risk of CVD in recent years. Adult reports suggest that endothelial dysfunction is one of the earliest indicators of atherosclerosis.[5] Contemporary studies have also reported that endothelial dysfunction occurs in children with KD, even without coronary abnormalities during the acute phase.[6] Aortic distensibility and stiffness, flow-mediated dilatation (FMD) of the brachial artery, and carotid intima-media thickness (CIMT) measurements are studied and used for detecting early functional changes of the arterial wall, and have been shown to be related to atherosclerosis risk in various patient groups.[7,8] Some of these indices, such as FMD and stiffening of aorta, have been previously studied in patients with KD, and have been found to be increased. On the other hand, inconsistent results with CIMT have also been reported.[9]

The role of chronic inflammation in the development of atherosclerosis and cardiovascular risk in adult patients is known. High-sensitivity C-reactive protein (hs-CRP) is a marker of inflammation, and is reported to increase in line with the degree of clinical atherosclerosis. It is demonstrated that hs-CRP and elastin values are significantly related to cardiovascular risk factors such as age, body mass index, and hyperlipidemia.[10,11] Elastin is another biomarker related to vascular aging and atherosclerosis.

In this study, we combined the echocardiographic non-invasive measurements and biomarkers for evaluation of vascular functions long after KD, in order to investigate whether these patients have an increased cardiovascular risk compared to the normal population.

METHODS

Patients

This study was conducted in the outpatient clinics of pediatric cardiology between August 2013 and December 2014, in Marmara University School of Medicine, İstanbul, Turkey. Twenty-six patients followed-up with a history of KD, and were identified retrospectively from the clinics' database. All participants in the Kawasaki group had been diagnosed in our clinics during the acute phase, on the basis of international guidelines.[12] All the patients had received IVIG treatment during the acute phase of the disease. The mean duration of IVIG treatment after the onset of the disease was 6.92 $\pm$ 1.49 days. The follow-up period for Kawasaki patients was at least 1 year after the diagnosis, to minimize a potential confounding influence related to subacute inflammation.[13] The control group consisted of 26 children with similar age and sex, referred to the pediatric cardiology clinic with non-anginal chest pain or innocent murmur, and found to have no cardiac pathology at physical examination or echocardiography. Children with hypertension, hyperlipidemia, diabetes, obesity, or any systemic disease capable of causing an increased risk for atherosclerosis were excluded. Children who did not cooperate or whose parents did not consent were also excluded. Ethics committee approval was received for this study from the Ethical Committee of Marmara University, numbered 09.2013.0192 and dated June 28, 2013. All the participants' parents provided written informed consent to participate.

All the patients in the study group were apparently healthy, and no sign of cardiac disease or permanent sequelae related to KD were observed during the research period. All participants underwent a complete physical examination. All the patients' physical examination findings, weight and height measurements, and systolic–diastolic blood pressures were recorded. The mean value of 3 consecutive blood pressure measurements was accepted as the final value.

Blood Sampling and Analysis

Serum blood lipid values, complete blood count (CBC), and erythrocyte sedimentation rate (ESR) were obtained on the day of the study.

Plasma elastin values were measured with the sandwich enzyme-linked immunosorbent assay (Cloud-Clone Corp., USA). The within-run precision values were <10% and between-run precision values were <12%, for low, middle, and high levels of elastin, as specified by the manufacturer. The minimum detectable level of elastin was 0.18 ng/mL.

Plasma hs-CRP levels were measured using hs-CRP enzyme immunoassay (Biomerica, Inc., CA, USA). The within-run precision values were <17.5% and the between-run precision values were <20%, for low, middle, and high levels of hs-CRP, as specified by the manufacturer. The minimum detectable level of hs-CRP was 0.1 mg/L.

Echocardiography

All participants underwent 2-D and M-mode studies, using a Philips IE33-model echocardiography device (Philips Medical Systems, Andover, MD, USA) with a 5-MHz sector and L-11-MHz linear transducers. All the studies were performed by the same physician. The end-systolic/end-diastolic diameters of the left ventricle (LVESD/LVEDD), end-diastolic diameter of posterior wall (LVPWDD), and the left atrial and aortic root diameters were measured. The systolic functions of the left ventricle were calculated by the M-mode echocardiographic procedure. The measures were defined with standard procedures, according to the suggestions of the American Society of Echocardiography.[14]

The systolic–diastolic aortic diameters were measured at multiple segments, namely the sinus of Valsalva, the sinotubular junction, the isthmus, the ascending aorta 3 cm distal to the aortic annulus, the proximal aortic arch between the truncus brachiocephalicus and the left carotid artery, and the abdominal aorta at the diaphragm level, with 2-D echocardiography at the end-diastolic phase simultaneously with the tip of the R-wave, and at the end-systolic phase simultaneously with the end of the T-wave at electrocardiography (Figure 1).The average of 3 consecutive beats was

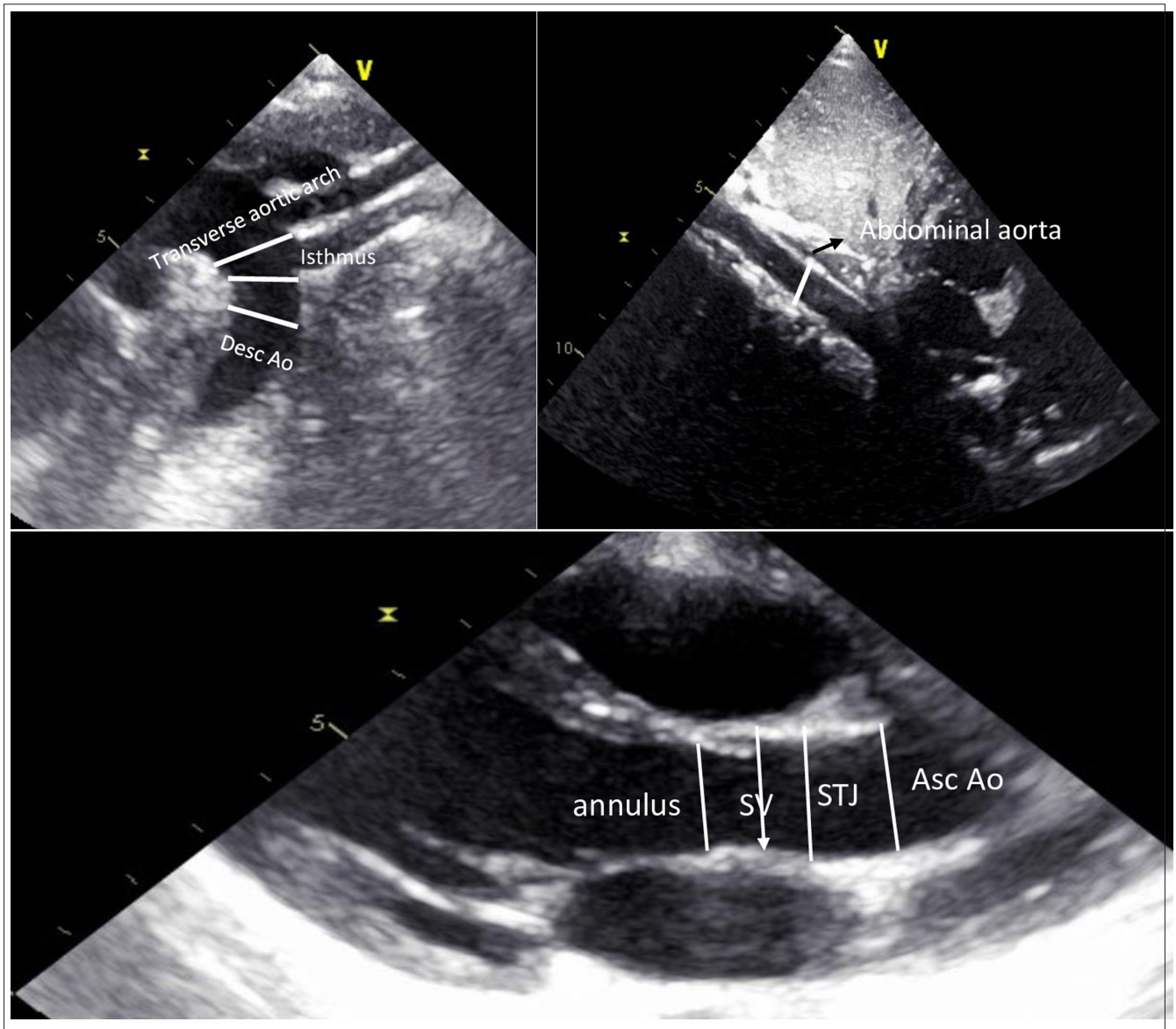

Figure 1. Measurements of aortic diameters in echocardiographic images.

recorded, and the diameters were indexed to the height of the patient.[14] All aortic measurements were obtained as previously described by Lacombe et al.[14,15] The stiffness and distensibility parameters were calculated using the formula:

$$\text{Aortic strain} = 100 \times (\text{Systolic dimension} - \text{Diastolic dimension}) / \text{Diastolic dimension}$$

$$\text{Aortic stiffness index (SI)} = \text{natural logarithm}(\text{Systolic blood pressure/Diastolic blood pressure}) / [\text{Systolic dimension} - \text{Diastolic dimension} / \text{Diastolic dimension}]$$

$$\text{Aortic distensibility} = 2 \times (\text{Systolic dimension} - \text{Diastolic dimension}) / [(\text{Systolic blood pressure} - \text{Diastolic blood pressure}) \times \text{Diastolic diameter}]$$

Carotid Ultrasound Studies

The common carotid artery (CCA) images used for assessment were acquired while the child was in supine position with the head turned to the left. Images were obtained at the end-diastolic phase simultaneously with the tip of the R-wave on electrocardiogram. The neck vessels were first demonstrated in a cross-sectional plane, after which the transducer was rotated clockwise to a longitudinal plane. Measures were acquired when the longitudinal distance of the CCA walls were visible for at least 10 mm on both sides. Measurement of CIMT was performed at the far wall of the CCA. CIMT was described as the distance between 2 bright lines measured edge to edge. An average CIMT value was obtained from 3 separate video-loop measurements.[16]

The stiffness 'β' and the pressure-elastic modulus (Ep) were calculated using the formulae (systolic blood pressure/diastolic blood pressure)/(difference in systolic and diastolic diameter/

diastolic diameter) and (pressure/diastolic diameter)/(difference in systolic and diastolic diameter), respectively.[17,18]

Brachial Artery Ultrasound Studies

All ultrasound studies were performed with a Philips IE33 echocardiography device (Andover, MD, USA) equipped with an L-11-MHz linear transducer. In order to reduce the effect of external stimuli, all studies were carried out in a quiet, temperature-controlled room (24°C to 26°C). The participant was laid supine on a couch in this room. The right brachial artery thickness was evaluated from B-mode ultrasound images at rest and during reactive hyperemia. Following a 10-minute rest, a straight, non-branching segment of the brachial artery above the antecubital fossa was visualized and analyzed in longitudinal position. Brachial artery diameter was initially recorded after the depth and gain settings were regulated. A pneumatic cuff was then inflated to above 50 mmHg on the upper arm for 5 minutes and then released. After cuff deflation, brachial artery thickness was measured at every 30 seconds for 3 minutes in the end-diastolic phase. FMD was calculated as the percentage change in diameter from baseline to the highest value after cuff deflation. The average of 3 sequential measures was accepted as the final measurement.[19]

The same echocardiographic and biochemical measurements were performed in the control group. The difference between the groups was analyzed.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM SPSS Corp.; Armonk, NY, USA) program. The variables were compared using the Student's *t*-test and the Mann–Whitney *U*-test for normally and non-normally distributed variables, respectively. Categorical variables were analyzed with the chi-square and Fisher's exact test. In the cases where both variables were normally distributed, Pearson's test was used for calculating the correlation coefficients and their significance. In the cases where at least 1 variable was not normally distributed, Spearman's test was used. The results were evaluated at a 95% CI, and *P* values <.05 were regarded as significant.

RESULTS

Patient Characteristics

The study group consisted of 5 girls (19.2%) and 21 boys (80.8%), and the healthy control group consisted of 4 girls (15.4%) and 22 (84.6%) boys. Their ages ranged between 4 and 19 years in the patient group (median = 7, mean ± SD = 8.32 ± 3.7), and between 4 and 16 years in the control group (median = 9.5, mean ± SD = 8.96 ± 3.5). No statistically significant differences were present between the groups in terms of age, height, weight, or systolic and diastolic blood pressures (Table 1).

The mean age at diagnosis in the KD group was 4.88 ± 2.71 years (range: 1-13 years). The follow-up period in the patient group was 3.48 ± 2.47 years (range: 1-15 years). In the study, 10 children (40%) had cardiac involvement during the acute phase, in the form of transient coronary dilatation in 6 patients (23%), mitral valve regurgitation in 2 (7.69%) patients, and pericarditis and systolic dysfunction of the left ventricle in 2 (7.69%) patients. None of the patients had persistent coronary aneurysm. All patients had been treated with IVIG 2 g/kg, and salicylates 75-80 mg/kg just after diagnosis, and 3 (11.5%) patients were IVIG-resistant and had received another dose of IVIG.

Table 1. Clinical and Laboratory Features of the Patients and the Control Group During the Study

	Patients (*n* = 26)	Control (*n* = 26)	*P*
Female/male	5/21	4/22	1.00[a]
Age (years)	8.19 ± 3.8	8.96 ± 3.44	.407[b]
Weight (kg)	30.65 ± 17.72	29.38 ± 10.2	.595[b]
Height (cm)	128.5 ± 20.1	129.9 ± 16.4	.810[c]
Heart rate (beat/min)	87.6 ± 13.2	89.1 ± 12.8	.680[c]
SBP (mmHg)	100.88 ± 9.83	99.69 ± 8.76	.804[b]
DBP (mmHg)	64.46 ± 7.43	62.42 ± 6.6	.322[b]
Hb (g/dL)	12.4 ± 1.14	12.7 ± 0.74	.289[c]
WBC ($mm^{3)}$	7326.92 ± 1655.43	7500 ± 2209.88	.934[b]
Plt (mm^3)	305423.08 ± 64770	305384.62 ± 69516	.998[c]
ESR (mm/h)	13.23 ± 10.85	14.5 ± 11.21	.532[b]
Total chol. (mg/dL)	168.27 ± 33.23	161.62 ± 29.75	.450[c]
HDL (mg/dL)	52.30 ± 11.12	52.69 ± 7.54	.627[b]
LDL (mg/dL)	99.65 ± 31.10	95.08 ± 25.08	.562[c]
Triglyceride (mg/dL)	80.92 ± 41.08	66.96 ± 34.89	.136[b]
hs-CRP (ng/mL)	2.13 ± 6.65	0.98 ± 1.49	.449[b]
Elastin (ng/mL)	8.27 ± 6.87	11.66 ± 10.27	.105[b]
Duration of KD follow-up (years)	3.48 ± 2.47 (1-15)		

SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin; WBC, white blood cell; mm^3, cubic millimeter; Plt, platelet; ESR, erythrocyte sedimentation ratio; mm/h, millimeter/hour; total chol., total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; KD, Kawasaki disease.
[a]Chi-square–Fisher's exact test.
[b]Mann–Whitney *U*-test.
[c]Student's *t*-test.

Laboratory Findings

No statistically significant difference in terms of basic laboratory findings such as CBC, ESR, and blood lipids was found between the patients and the control group (Table 1). The hs-CRP values were higher and serum elastin values lower in the patient group than in the control group. However, the differences were not statistically significant (P = .449 and P = .105, respectively) (Table 1). Positive correlation was found between the hs-CRP levels and stiffness of the abdominal aorta and distensibility of the ascending aorta.

We analyzed the correlation in the laboratory findings during the acute phase of KD (Table 2) with echocardiographic findings, to identify the predictive factors for sclerotic change, but there was no correlation between the parameters.

Echocardiographic Measurements

The M-mode measurements showed no differences between the patient and control groups in terms of LVEDD, LVPWDD, and left atrial and aortic diameters (Table 3). Systolic and diastolic diameters of the aortic root (sinus of Valsalva, sinotubular junction, isthmus, and ascending aorta), and the aortic arch did not vary significantly between the 2 groups.

Table 2. Laboratory Findings of the Patients with Kawasaki Disease During the Acute Phase of the Disease

Data	Patients (n = 26)
Age at Kawasaki disease diagnosis (years)	4.88 ± 2.71
WBC (mm^3)	13973 ± 5056.13
Hb (g/dL)	11.14 ± 1.17
Plt (mm^3)	435307.6 ± 233302
ESR (mm/h)	67.56 ± 24.61
CRP (mg/L)	62 ± 60.03
Albumin (g/dL)	3.08 ± 0.68
Na (mEq/L)	132.6 ± 2.53
AST (U/L)	47.57 ± 24.46
ALT (U/L)	53.5 ± 47.58

WBC, white blood cell; mm^3, cubic millimeter; Hb, hemoglobin; Plt, platelet; ESR, erythrocyte sedimentation ratio; mm/h, millimeter/hour; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine amino transferase.

Table 3. Echocardiographic Characteristics of the Patient and Control Group

	Patients Group (n = 26)	Control Group (n = 26)	P
LVPWdd (cm)	0.81 ± 0.60	0.69 ± 0.27	.145[a]
LVEDD (cm)	3.75 ± 0.99	3.81 ± 0.48	.390[a]
IVSdd (cm)	0.731 ± 0.11	0.65 ± 0.10	.160[b]
LA (cm)	2.42 ± 0.43	2.27 ± 0.46	.181[a]
Aortic annulus (cm)	2.13 ± 0.39	1.97 ± 0.36	.436[b]
EF (%)	67.61 ± 5.4	67.42 ± 5.36	.741[a]
SF (%)	35.69 ± 4.54	36.76 ± 4.4	.569[a]
Mitral E (m/sn)	0.97 ± 1.28	0.97 ± 1.01	.422[a]
Mitral A (m/sn)	0.66 ± 0.13	0.63 ± 0.15	.093[a]
IVRT (msn)	72.65 ± 15.99	73.23 ± 9.93	.438[a]
DT (msn)	139.30 ± 28.90	136.89 ± 38.50	.252[a]

LVPWdd, left ventricle posterior wall end-diastolic diameter; LVEDD, left ventricle end-diastolic diameter; IVSdd, interventricular septum end-diastolic diameter; LA, left atrium; EF, ejection fraction; SF, shortening fraction.
[a]Mann–Whitney U-test.
[b]Student's t-test.

Aortic Elasticity Parameters

The stiffness index (SI) values of the aortic arch, isthmus, and abdominal aorta were higher in Kawasaki patients than in the control group (P = .01, P = .009, and P = .004, respectively). The sinus of Valsalva, sinotubular junction, aortic arch, and ascending aorta were less distensible in the patient group than in the control group (P = .006, P = .0001, P = .003, P = .002, and P = .001, respectively). The strain rates in the aortic arch and isthmus were lower than in the control group (P = .001 and P = .01, respectively) (Table 4). Age of the patients correlated negatively to distensibility of the aortic arch and abdominal aorta, and positively to stiffness of the aortic arch (P = .009, r = −0.502; P = .046, r = −0.394 and P = .001, r = 0.649 respectively) (Figure 2). The duration of follow-up correlated positively to stiffness of the aortic arch (P = .006, r = 0.523) (Figure 3).

We also studied the correlation between age and elasticity of the aorta, stiffness of the CCA, FMD of the brachial artery, CIMT, and laboratory measurements in the control group. Only age correlated negatively to FMD of the brachial artery at 3 minutes (r = −0.407, P = .039).

Carotid Ultrasound Studies

The stiffness of the CCA was assessed using conventional stiffness "β" and the Ep was significantly higher in the Kawasaki group than the healthy control group (P = .01 for both). CIMT was also higher in the patient group, although the difference was not statistically significant (P > .05) (Table 5).

Flow-mediated Dilatation

The FMD values of the brachial artery at 1 and 3 minutes were lower in the patient group than in the healthy group, although the only significant difference was in the rate of dilatation of the brachial artery at 3 minutes (P > .05 and P = .01, respectively) (Table 5).

Compared to patients with and without cardiac involvement, none of the parameters studied differed significantly between the groups (P > .05).

DISCUSSION

KD is a generalized vasculitis that affects the entire arterial system, particularly the coronary arteries. Coronary artery dilatation, aneurysm formation, and thrombosis and stenosis of the affected coronary arteries may cause myocardial ischemia and infarction. Mild dilatation and small aneurysms may regress later than the acute phase of the illness, and cardiac sequelae are observed in 5-6% of patients despite treatment with IVIG.[3] This has been attributed to significant instability in the immunoregulatory system, resulting in coronary inflammation and coronary artery abnormalities in some patients. Additionally, recent reports have shown that KD causes detrimental effects on coronary artery functions, even years after acute presentation with or without coronary abnormalities.[6] Some studies have also suggested a high risk of atherosclerosis even in children who have never developed coronary artery involvement. Previous studies have also implicated

Table 4. Aortic Elasticity Parameters of the Patient and Control Group

	KD (*n* = 26)	Control (*n* = 26)	*P*[a]
Sinus of Valsalva			
Strain (%)	3.59 ± 2.46	4.91 ± 4.16	.08
DIS ($cm^2\ dyn^{-1}\ 10^{-6}$)	3.40 ± 3.33	5.87 ± 1.53	.006
SI	0.68 ± 0.55	0.57 ± 0.59	.24
Sinotubular junction			
Strain (%)	4.33 ± 3.38	5.57 ± 5.44	.068
DIS ($cm^2\ dyn^{-1}\ 10^{-6}$)	2.52 ± 2.40	5.87 ± 1.30	.0001
SI	0.75 ± 0.78	0.60 ± 0.72	.23
Arcus aorta			
Strain (%)	5.80 ± 4.13	11.56 ± 6.12	.001
DIS ($cm^2.dyn^{-1}.10^{-6}$)	4.90 ± 2.95	6.42 ± 3.15	.039
SI	0.63 ± 0.75	0.18 ± 0.10	.01
Ascending aorta			
Strain (%)	7.57 ± 5.07	8.40 ± 4.65	.27
DIS ($cm^2\ dyn^{-1}\ 10^{-6}$)	3.85 ± 2.30	5.82 ± 1.45	.002
SI	0.37 ± 0.37	0.32 ± 0.37	.32
Isthmus			
Strain (%)	5.20 ± 4.16	9.31 ± 5.17	.01
DIS ($cm^2\ dyn^{-1}\ 10^{-6}$)	2.74 ± 1.93	5.36 ± 3.66	.001
SI	0.58 ± 0.48	0.30 ± 0.36	.009
Abdominal aorta			
Strain (%)	7.24 ± 5.31	8.88 ± 4.44	.129
DIS ($cm^2\ dyn^{-1}\ 10^{-6}$)	5.37 ± 3.96	6.44 ± 3.5	.07
SI	0.34 ± 0.20	0.19 ± 0.10	.04

DIS, distensibility; SI, stiffness index.
[a]Student's *t*-test.

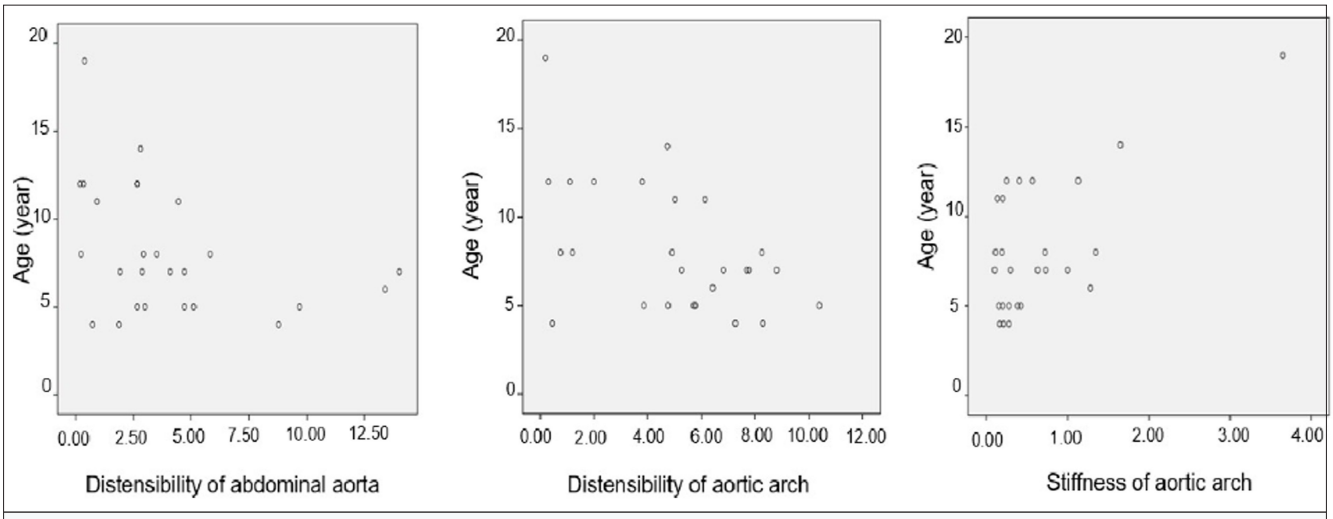

Figure 2. Correlations between age and aortic elasticity parameters.

factors such as endothelial dysfunction, proatherogenic lipid profiles, and increased arterial stiffness, in the development of atherosclerosis.[20]

Recent reports have demonstrated that the measurement of aortic stiffness, distensibility, and strain rate are useful in the early detection of atherosclerosis. The abdominal aorta becomes stiffer with age, and stiffness is more prominent in the presence of obesity, hypertension, atherosclerosis, and in patients with Marfan syndrome or KD, which are all accepted risk factors for atherosclerotic CVD.[21-23] Oyamada et al.[24] reported a higher aortic SI in 75 children with KD, compared to a control group. Those authors also noticed decreased aortic distensibility and aortic strain in these patients. Similarly, Gupta et al.[25] found increased stiffness and lower distensibility of the abdominal aorta. The current study observed a significant increase in the SI and decreased distensibility-strain rates in various aortic segments, not solely in the abdominal aorta as in some previous studies in patients with KD. In addition, we observed significant positive correlation between stiffness of the aortic arch

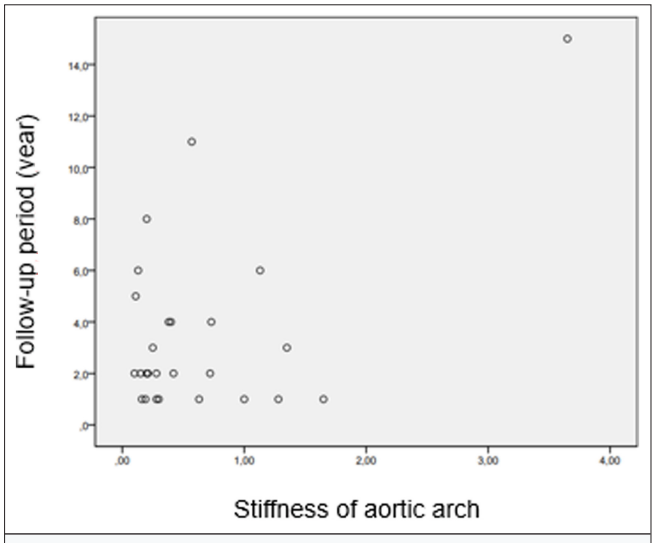

Figure 3. Correlations between follow-up period and aortic elasticity parameters.

Table 5. Carotid Ultrasound and Flow-Mediated Dilatation Parameters

	Patients Group	Control Group	*P*
CIMT (mm)	0.51 ± 0.08	0.49 ± 0.05	.713[a]
Carotid β stiffness	0.94 ± 0.35	0.71 ± 0.34	.01[b]
Carotid Ep	40.31 ± 18.24	27.45 ± 12.65	.01[a]
FMD first minute (%)	4.7 ± 2.81	6.72 ± 5.81	.162[a]
FMD third minute (%)	7.08 ± 3.86	10.40 ± 4.00	.01[a]

CIMT, carotid intima media thickness; FMD, flow-mediated dilatation; Ep, pressure-elastic modulus.
[a]Mann–Whitney *U*-test.
[b]Student's *t*-test.

and the current ages of the patients, and also the duration of the disease. Furthermore, patient age had a significant negative correlation with the distensibility of both the aortic arch and abdominal aorta. There are other adult and pediatric studies demonstrating same correlations with patient age and follow-up duration.[15,25] It is known that arterial stiffness increases and distensibility decreases with increasing age; therefore, other studies are needed in order to demonstrate whether this correlation is due to the effect of KD.

FMD is a useful indicator of endothelial dysfunction. The degree of endothelial function is a known predictor of cardiovascular outcomes in adults.[26] The study population in most previous studies has included adolescents. We demonstrated lower FMD in children with KD, compared to healthy children. Ishikawa et al.[27] reported significantly lower FMD in 9 patients with coronary artery lesions than in 15 patients without coronary anomalies; the values in both groups were lower than those of the healthy control group.

Increased CIMT is another useful marker for atherosclerosis risk in adults and adolescents. Significantly higher CIMT in patients with KD (mean age 8.6 years) was reported previously. The follow-up period from diagnosis of KD to the time of the study was 5.8 years.[28] In our report, CIMT was higher in patients with a history of KD; however, the difference was not statistically significant, probably due to shorter follow-up duration. Although conflicting results have been reported in CIMT changes in children with KD, a previous study noticed no differences in CIMT among patients with varying severities of coronary artery lesions or between patients and controls.[29] Dietz et al.[30] showed children with a history of KD complicated by giant coronary artery aneurysm to be associated with increased CIMT. Another study investigated the SI and Ep of CCA together with CIMT, in order to evaluate the risk of atherosclerosis in 75 patients with KD, and reported insignificantly higher values compared to the healthy control group.[31] In our study; both the SI and Ep of the CCA had increased significantly in the patient group compared to the control group. These findings also indicate an increased risk for atherosclerosis in this patient group.

Hs-CRP and elastin are indicators of inflammation, and also good predictors of atherosclerosis risk and acute coronary events. Some recent studies in an apparently healthy population have indicated that hs-CRP values are importantly related to cardiovascular risk factors such as age, body mass index, smoking, and hyperlipidemia. Many earlier studies have identified significantly increased serum CRP levels in the acute stage of KD.[10] Dedeoğlu et al.[32] observed high CRP levels during the acute phase of KD to be associated with coronary artery aneurysms. KD with persistent coronary artery lesions was subsequently shown to be independently associated with levels of hs-CRP in school-age children.[11,33] Adult studies have also described serum elastin levels and activity as markers of vascular aging and atherosclerosis. It has also been suggested that serum elastin levels decrease significantly with age in men, and are not affected by smoking in either sex. However, to the best of our knowledge, studies investigating serum elastin levels and vascular complications in children are limited to diabetic patient groups. These have suggested that increased values of serum elastin are indicative of diabetic vascular complications.[34] Even though our study shows a positive correlation between hs-CRP with the stiffness of abdominal aorta and the distensibility of the ascending aorta, the differences between patient and control groups in terms of these parameters are not statistically significant. Therefore, further studies are needed for clarification of these issues.

This study has certain limitations. To our knowledge, this is the first study combining all echocardiographic measurements and biomarkers indicating cardiovascular risk in patients with previous KD. However, the number of children in the sample group was small and the follow-up period was relatively short for the accurate evaluation of increased risk for atherosclerotic CVD.

In conclusion, we observed increased aortic–CCA stiffness, decreased aortic distensibility, and FMD of the brachial artery in patients with a history of KD. These findings may suggest impaired arterial functions and an elevated risk for atherosclerotic CVD following KD. Further investigations, including

long-term outcomes with larger patient groups, close monitoring during adulthood, and elimination of other avoidable risk factors are needed in this patient group.

Ethical Committee Approval: Ethics committee approval was received for this study from the Ethical Committee of the Marmara University, numbered 09.2013.0192 and dated June 28, 2013.

Informed Consent: Informed consent was obtained from the parents of the patients who participated in this study.

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