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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