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Original article

Analysis of arterial function in adults with a history of Kawasaki disease

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ABSTRACT

Background and purpose: It remains controversial whether Kawasaki disease (KD) is a risk factor for the early onset of atherosclerosis.

The purpose of the present study was to assess endothelial function and arterial stiffness as markers of the early onset of atherosclerosis in adult patients with a history of KD.

Methods and subjects: We compared 14 adult patients with a history of KD with 41 healthy controls. To assess arterial endothelial function, we measured the reactive hyperemia-peripheral arterial tonometry (RH-PAT) index and augmentation index adjusted to 75 bpm (AIx@75) using the Endo-PAT 2000 (Itamar Medical, Caesarea, Israel). In addition, we analyzed medical history, blood pressure, lifestyle habits, and atherosclerosis-related serum biochemical markers [asymmetric dimethylarginine, adiponectin, lipoprotein (a), cholesterols, atherogenic index of plasma].

Results: There was no difference between the KD and control groups with regard to the RH-PAT index values (2.10 ± 0.43 and 1.84 ± 0.49, respectively; $p = 0.19$). However, in the KD group, the RH-PAT index values were negatively correlated with the febrile period in the acute phase of disease ($r^2 = 0.458$, $p = 0.048$). In addition, the AIx@75 values were higher in KD patients compared to healthy controls ($-7.69 \pm 11.86\%$ and $-15.87 \pm 8.72\%$, respectively; $p = 0.01$). No significant differences existed between the KD and control groups with regard to the serum biomarkers of atherosclerosis.

Conclusions: We speculate that endothelial dysfunction in former KD patients is affected by the febrile period of the acute phase, and antiplatelet drugs may improve endothelial function. The increased arterial stiffness of patients caused by post-inflammatory fibrotic changes in the arterial wall indicates that adults with a history of KD have an increased risk of developing atherosclerosis.

Introduction

Kawasaki disease (KD) is acute systemic vasculitis that occurs predominantly in infants and during early childhood. More than 12,000 individuals were newly diagnosed with KD in Japan in 2010 and the average annual incidence rate was 222.9 per 100,000 children aged 0–4 years in 2009–2010 [1]. As of 2006, the total number of KD patients reported since 1970 was 225,682. Of those patients, more than 90,000 had already reached adulthood [2].

KD is typically self-limited, and a good prognosis is generally expected for patients who recover from KD without coronary sequelae. However, some studies have reported that some former KD patients without coronary artery lesions developed ischemic heart disease [3]. Therefore, a history of KD has recently been indicated as a possible risk factor for the early onset of atherosclerosis.

Numerous reports have demonstrated the association between KD and arteriosclerosis [4–13]. However, the studies primarily investigated children or adolescents. Therefore, it remains controversial whether KD is a risk factor for the onset of atherosclerosis in adults.

Because endothelial dysfunction is closely related to arteriosclerosis risk factors [14–16], examination of endothelial function can detect early-stage arteriosclerosis. The endothelium plays a crucial role in the maintenance of vascular tone [17]. Endothelium-derived nitric oxide (NO) is a potent endogenous vasodilator [18], which is released in response to shear stress, and plays an important role in flow-mediated dilatation [19]. The functional assessment of endothelial function is based on the physiological dilatation of the artery in response to increased blood flow [20].

However, forearm flow-mediated vasodilation (FMD) results can vary due to technical problems. To evaluate endothelial dysfunction, reactive hyperemia peripheral arterial tonometry (RH-PAT) is conducted by measuring changes in the digital pulse

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volume during reactive hyperemia; this technique is non-invasive, automatic, quantitative, and reproducible [21,22].

Another vascular alteration that precedes atherosclerosis is increased rigidity of the arterial wall. Several indices have been developed to assess arterial stiffness, including aortic pulse wave velocity (PWV) and the augmentation index (AIx) [23,24]. AIx is associated with cardiovascular risk [25], and is an independent predictor of cardiovascular events [23].

In addition, the biochemical marker, asymmetric dimethylarginine (ADMA), acts as an endogenous inhibitor of endothelial nitric oxide synthase (NOS) by competing with L-arginine as a NOS substrate. ADMA reduces NO production, thereby leading to endothelial dysfunction and cardiovascular events. Studies have shown that increased concentrations of ADMA found elevated plasma ADMA concentration has been identified as an independent risk factor for the progression of atherosclerosis and cardiovascular death [26,27].

To assess the long-term possibility of early-onset atherosclerosis after KD, we examined endothelial function using RH-PAT, arterial stiffness using AIx, and biochemical markers in adult patients late after the onset of KD.

Materials and methods

Study subjects

This study included 14 adult patients referred to as the KD group [aged 21–41 years, mean ± standard deviation (SD): 31.5 ± 5.5 years] and 41 age-matched subjects referred to as the control group. All subjects in both groups were Japanese, non-smokers (defined as individuals who had never smoked), were not born prematurely, and had no medical history of hypertension, hyperglycemia, or hypercholesterolemia. In addition, they did not have family histories of hereditary diseases such as homocystinuria or familial hypercholesterolemia. The KD group was recruited from the Juntendo University Hospital, the Koshigaya Municipal Hospital, and the Parents Association of Kawasaki Disease (interval time: 28.6 ± 5.6 years). Eleven of these patients had persistent coronary aneurysms, whereas one had aneurysms that had regressed. The maximum diameter of the dilated coronary arteries was more than 8 mm in 5 patients [giant aneurysms (ANl)], 4–8 mm in 5 patients [medium aneurysms (ANm)], and less than 4 mm in 2 patients [small aneurysms (ANs) or dilatation (Dil)]. Four patients had local stenosis (LS), 2 patients had mild coronary stenosis (one had 90% stenotic lesion and the other had 75%), and 2 patients had moderate coronary stenosis (they had 25%) [28]. Three of the KD patients did not have coronary complications. Three KD patients had received intravenous immunoglobulin therapy during the acute phase of illness, while 10 were also receiving long-term aspirin maintenance therapy. One of the 10 subjects was taking clopidogrel as a maintenance therapy. All the KD patients were asymptomatic and required no coronary artery interventions. The control subjects were healthy volunteers who willingly participated in this study. This study was approved by the ethics committee of the Juntendo University Hospital. Informed consent for the research protocol was obtained from all subjects.

Study protocol

The subjects were advised against consuming food and drink (except for water) overnight, and against performing heavy exercise on the day before the examination. Venous blood withdrawal was performed in a quiet examination room at 23–26 °C in the early morning.

We obtained the past history for KD in all subjects, measured blood pressure automatically from the right arm, and performed a physical examination as described below. After the physical examination, blood analysis was performed.

Assessment of endothelial function

RH-PAT was performed using the Endo-PAT2000 method (Itamar Medical Ltd., Cesarea, Israel), which assesses the magnitude of RH at the finger-tip as a measure of microvascular endothelial function. The participants were placed in the supine position with both hands resting at the same level. Specific peripheral arterial tonometry (PAT) finger probes for recording the digital pulse volume curves (PAT signal) were placed on 1 finger of each hand and a blood pressure cuff was placed on 1 upper arm (study arm), while the other arm served as a control (control arm). After continuous recording of the PAT signal from both hands for 10 min, the blood pressure cuff on the study arm was inflated to whichever pressure would be higher, i.e. 200 mm Hg or 60 mm Hg plus systolic blood pressure for 5 min. Subsequently, the blood pressure cuff was rapidly deflated to induce RH in the forearm and hand while the PAT signal continued to be recorded for 10 min. The PAT signal data were analyzed automatically in an operator-independent manner by the Endo-PAT2000 device. Briefly, as a measure of the extent of RH, the RH-PAT index was calculated as the ratio of the average amplitude of the PAT signal over a 1-min time interval starting 1 min after cuff deflation divided by the average amplitude of the PAT signal of the 3.5-min period before cuff inflation (baseline), which was then multiplied by a baseline correction factor. The RH-PAT index values from the study arm were then normalized to the control arm to compensate for potential systemic changes. An RH-PAT index value less than or equal to 1.67 was used as a cut-off value to diagnose endothelial dysfunction [29].

Assessment of arterial stiffness

Arterial stiffness was measured by AIx using PAT technology. AIx is defined as an increment in pressure after the first systolic shoulder to the peak of aortic pressure and is expressed as a percentage of aortic pulse pressure. Pressure sensors within this particular finger probe capture the beat-by-beat finger pulse wave amplitude (PWA), which is then filtered, amplified, and graphically displayed on a computer screen. A computerized algorithm was generated to automatically identify peak pressures and the inflection point. The PAT-AIx is calculated by averaging the PWA data over a period of 3.5 min, and is defined as the difference between the second and first systolic peaks expressed as a percentage of the pulse pressure. The AIx adjusted to 75 bpm (AIx@75) was calculated by adjusting the AIx to a 75 beats/min variable, as this measurement is influenced by heart rate.

Blood sampling and analysis

Serum ADMA, adiponectin, lipoprotein (a), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), glucose, and insulin levels were evaluated. Using enzyme-linked immunosorbent assays (ELISA), we measured ADMA and adiponectin (ADMA, Immundiagnostik AG, Bensheim, Germany; adiponectin, Sekisui Medical, Tokyo, Japan). In addition, we calculated the homeostasis model assessment-insulin resistance (HOMA-IR) as the level of glucose tolerance and the atherogenic index