Echo-Doppler Assessment of Arterial Stiffness in Pediatric Patients with Kawasaki Disease

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Background: There is growing evidence to suggest increased arterial stiffness in patients with a history of Kawasaki disease (KD). Pulse-wave velocity (PWV) is the most validated measure of arterial stiffness. The aim of this study was to determine if aortic PWV is increased in children with KD.

Methods: This was a retrospective cohort study. The study cohort was composed of 42 patients with KD (mean age, 9.7 ± 2.0 years) and 44 age-matched control subjects. The primary measure was aortic PWV. Secondary measures included characteristic impedance (Zc), input impedance (Zi), elastic pressure-strain modulus (Ep), and β stiffness index and the following measures of left ventricular size and function: end-diastolic and end-systolic dimensions, wall thickness in diastole and systole, mass, shortening and ejection fractions, mean velocity of circumferential fiber shortening, and stress at peak systole. The appropriate measures were indexed to body surface area. The aortic stiffness and impedance indexes were derived using an echocardiography-Doppler method.

Results: Height, weight, body mass index, and body surface area were similar between the groups. PWV was higher in patients with KD compared with controls (495 vs 370 cm/sec, $P = .0008$). Zc, Ep, and β stiffness index were higher in patients with KD, but the difference was not statistically significant. Left ventricular dimensions were all within normal limits, with no differences between the groups. Patients with KD had lower stress at peak systole compared with controls (55 vs 64 g/cm^2, $P = .01$). There was a significant association between the length of time between the initial diagnosis and testing with PWV ($r = 0.32$, $P = .04$) and Zi ($r = -0.38$, $P = .01$) in patients with KD. There was no significant association between the arterial stiffness indexes (PWV, Zi, Zc, Ep, and β stiffness index) and length of fever, age at KD diagnosis, or heart rate. Logistic regression analysis revealed no association between coronary artery lesion classification and length of fever, day of illness at first treatment, age at KD diagnosis, or any of the arterial stiffness indexes. In the control group, there were significant associations between age and heart rate ($r = -0.48$, $P = .001$), Zi ($r = -0.55$, $P < .0001$), Zc ($r = -0.66$, $P < .0001$), and β stiffness index ($r = -0.31$, $P = .04$). There was an association between heart rate and Zc ($r = 0.44$, $P = .003$) but no association between heart rate and PWV, Zi, Ep, or β stiffness index.

Conclusions: Arterial stiffness was increased in children with KD. There was no association between acute-phase KD coronary involvement and PWV. This implies that patients with KD may be at increased cardiovascular risk in the future. (J Am Soc Echocardiogr 2013;26:1084-9.)

Keywords: Kawasaki disease, Pulse-wave velocity, Vascular function, Echocardiography Doppler

Kawasaki disease (KD) is the most common acquired heart disease encountered in children in developed countries. It was first described by Tomisaku Kawasaki in 1967 in Japan.[1] Today, it is seen frequently in >60 countries worldwide, with the highest incidence in Japan, reaching an average annual incidence rate of 216.9 per 100,000 children aged 0 to 4 years.[2] In the United States, >5,500 pediatric hospital admissions each year are attributed to KD.[3] KD affects small to medium-sized blood vessels and causes multisystem inflammatory disease.[1] The most serious complications associated with KD are the development of coronary aneurysms, coronary ischemia, and thrombosis. During the acute phase of KD, up to 11% of children develop valvular lesions or coronary artery lesions (CALs), with only 3% developing cardiac sequelae 1 month after the onset of KD. Of these patients, 2% develop coronary dilatation, 1% develop coronary aneurysms, and <1% develop valvular lesions, coronary stenoses, or myocardial infarctions.[2] Less frequently, KD causes pancarditis, with involvement of the pericardium, myocardium, and endocardium. During the acute phase, KD leads to generalized vasculitis throughout the body. The inflammation starts in the vascular endothelium and the outer adventitia and spreads toward the media and the perivascular space. This can lead to a proliferation of intimal cells and a range of pathologic changes, including destruction of the elastic interna, vessel stenosis, aneurysm, and thrombus formation.[4]

A number of follow-up studies have documented abnormal endothelial function and reduced vascular elasticity in patients with KD.[5-7]

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Abbreviations

AOcsa = Aortic annular cross-sectional area

AOd = End-diastolic aortic dimension

AOflow = Peak aortic flow

AOs = End-systolic aortic dimension

BPd = Diastolic blood pressure

BPs = Systolic blood pressure

CAL = Coronary artery lesion

EF = Ejection fraction

Ep = Elastic pressure-strain modulus

KD = Kawasaki disease

LV = Left ventricular

LVEDD = Left ventricular end-diastolic dimension

LVESD = Left ventricular end-systolic dimension

LVMi = Left ventricular mass index

MVCFc = Mean velocity of circumferential fiber shortening

PP = Pulse pressure

PWd = Diastolic posterior wall thickness

PWs = Systolic posterior wall thickness

PWV = Pulse-wave velocity

SF = Shortening fraction

σps = Stress at peak systole

TT = Transit time

Zc = Characteristic impedance

Zi = Input impedance

These findings have implications for long-term cardiovascular risk for hypertension, coronary artery disease, and stroke, as well as left ventricular (LV) size and diastolic and systolic function. Arterial stiffness can be evaluated using various techniques. Pulse-wave velocity (PWV) is the most validated measure of arterial stiffness.[8] It is the earliest and most sensitive predictor of cardiovascular risk.[9] PWV can be evaluated either by applanation tonometry or Doppler echocardiography. Various techniques have been used to show increased PWV in patients with a history of KD.[5,7,10] Our laboratory has described a simple, noninvasive Doppler echocardiographic technique for the assessment of the biophysical properties of the aorta, including PWV, characteristic impedance (Zc), input impedance (Zi), elastic pressure-strain modulus (Ep), and β stiffness index.[11,12] We hypothesized that children with a history of KD would have abnormal aortic stiffness and LV size and function on long-term follow-up compared with age-matched controls. To test these hypotheses, we assessed the biophysical properties of the aorta and measured LV size and function in a group of patients with established KD.

METHODS

Subjects

This was a retrospective cohort study conducted at British Columbia Children's Hospital (Vancouver, BC, Canada). Ethical approval was obtained from the University of British Columbia Children's and Women's Health Centre's Research Review Committee. The KD cohort was identified through the British Columbia Children's Hospital echocardiography database from January 1, 2002, to December 31, 2011. Since the first description of the Doppler echocardiographic method to assess the biophysical properties of the aorta in 2000,[13] our laboratory has included these measures in the protocol for patients undergoing comprehensive ventricular-vascular functional echocardiography.

Patients aged 2 to 18 years with detailed Doppler echocardiographic assessments including the PWV protocol ≥1 year after the diagnosis of KD were included. If a patient had undergone multiple studies, the most recent study was used for analysis. During the study period, 82 patients with KD were seen for long-term follow-up, and 42 with complete Doppler echocardiographic studies were included. We used subjects from our established healthy control Doppler echocardiography database. We included 44 subjects (aged 2–18 years) with no histories of acute or chronic illness or of hypertension, diabetes, vascular or inflammatory diseases, and congenital or acquired heart disease.

The relevant clinical data on all eligible patients with KD were reviewed. This included the date of KD diagnosis, the duration of fever, the mode of therapy (intravenous immunoglobulin, aspirin, and/or steroids) and the severity of coronary artery involvement, diagnosed by echocardiography or angiography. We recorded the worst CAL involvement during the acute phase using the American Heart Association's risk stratification approach: risk level 1 = no CAL, risk level 2 = mild ectasia, risk level 3 = isolated solitary small to medium-sized coronary artery aneurysm (>3 to <6 mm), risk level 4 = multiple aneurysms or one large or giant coronary artery aneurysm ≥6 mm, and risk level 5 = coronary artery obstruction.[14] Height, weight, and blood pressure were recorded before the Doppler echocardiographic assessment.

Doppler Echocardiography

All subjects underwent complete M-mode and two-dimensional Doppler echocardiographic assessment. The following measures were obtained LV end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD), diastolic posterior wall thickness (PWd), and systolic posterior wall thickness (PWs). We calculated shortening fraction (SF), ejection fraction (EF), mean velocity of circumferential fiber shortening (MVCFc), stress at peak systole (σps), and LV mass index (LVMi). Systolic blood pressure (BPs) and diastolic blood pressure (BPd) were measured over the right brachial artery using an auscultatory method. The standard criteria for normal and abnormal results were adopted from the American Society of Echocardiography recommendations.[15,16] Detailed coronary imaging was performed.

The aortic stiffness and impedance indexes were derived using a Doppler echocardiographic method described by our laboratory.[12] From a standard parasternal long-axis view using two-dimensional echocardiography, the aortic annulus was measured. In a high left or right parasternal view, an M-mode recording was made at a right angle, and the ascending aortic diameter was measured at end-diastolic and at maximum systolic dimensions. All measurements were made on two-dimensional and M-mode images using the trailing edge–to–leading edge method.

In a standard suprasternal long-axis view, an ascending aortic pulse-wave Doppler tracing was recorded, and the peak aortic velocity was measured. From the M-mode image of the ascending aorta, the end-diastolic aortic dimension (AOd) and end-systolic aortic dimension (AOs) were measured. The time from the QRS complex to the onset of the ascending aortic Doppler envelope (time 1) was measured. Maintaining the same transducer position, the pulse-wave Doppler sample volume was immediately placed as distal as possible in the descending aorta, and the time from the QRS complex to the onset of the descending aortic Doppler envelope (time 2) was measured. Using the same two-dimensional image, the aortic arch length between these two sample volume positions was obtained by summing serial measurements made with electronic calipers along the central axis of this curved segment of the aorta (Figure 1). All measurements were averaged over three consecutive cardiac cycles.