Altered Central Aortic Elastic Properties in Kawasaki Disease are Related to Changes in Left Ventricular Geometry and Coronary Artery Aneurysm Formation

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Background: Recent evidence has suggested that patients display altered arterial elasticity after Kawasaki disease (KD). However, changes in the elastic properties of the central aorta and their relevance to left ventricular geometry have not been studied in patients after KD with and without coronary artery aneurysms (CAAs).

Methods: Clinical and laboratory characteristics of 75 patients with KD were compared with those of 57 controls. The patients with KD included 17 patients with CAAs and 58 patients without CAAs. Values for aortic stiffness index, aortic distensibility, aortic strain, and left ventricular mass index (LVMI) were retrospectively obtained from echocardiographic measurements of the ascending aorta and left ventricle with noninvasive blood pressure evaluation.

Results: Systolic blood pressure, pulse pressure, LVMI, and aortic stiffness index were significantly higher and aortic distensibility and aortic strain significantly lower in patients with KD than in the controls. In patients with KD, age at the time of study, interval between the onset of KD and the initiation of this study, CAAs, and LVMI were significantly associated with aortic stiffness index, aortic distensibility, and aortic strain. Multivariate analysis revealed that CAAs and LVMI were independently relevant to aortic stiffness index and aortic distensibility.

Conclusions: The central aortas of patients after KD have altered elastic properties. CAAs and LVMI are independently correlated with central aortic elasticity. (J Am Soc Echocardiogr 2012;25:690-6.)

Keywords: Aortic stiffness, Kawasaki disease, Left ventricular mass

Kawasaki disease (KD) is an acute inflammatory syndrome, originally reported by Tomisaku Kawasaki[1] in 1967, that results in systemic vasculitis in children. Coronary artery aneurysms (CAAs) are the primary cause of morbidity and mortality in KD.[2] Although intravenous immunoglobulin therapy reduces the incidence of CAAs,[3] 4% of patients receiving this therapy still develop CAAs during the acute stage of KD.[4]

Previous studies have suggested that patients with histories of KD are predisposed to premature atherosclerosis.[5,6] Histopathologic examination of vascular changes in autopsied Japanese patients with KD have shown arterial changes in more than one arterial system (i.e., the elastic, musculoelastic, and midsize arteries).[7,8] Altered vascular function and elasticity in peripheral arteries have also become evident not only in patients with KD with CAAs but also in those without CAAs[5,9-12]; however, the differences in arterial elasticity between patients with KD with and without CAAs are still controversial.[10,13]

To date, aortic elasticity has been assessed mainly in the major aortic branches, and little attention has been given to central aortic elasticity in patients with KD. In adults, aortic stiffness is considered a risk factor for cardiovascular morbidity and mortality.[14-16] Furthermore, recent studies have shown that central aortic stiffness has a stronger association with cardiovascular disease than that of peripheral arterial segments.[17,18] Additional studies have shown that decreased vascular elasticity is also detected in children with cardiovascular risk factors.[19,20]

We hypothesized that alterations in the elastic properties of the ascending aorta influence arterial stiffness and therefore may influence both left ventricular remodeling and the formation of CAAs in patients after KD. To test this hypothesis, we compared indices of elastic properties of the ascending aorta in children and adolescents after KD with and without CAAs with those in controls. In addition, we examined relationships between indices of elastic properties of the ascending aorta and various clinical parameters, including left ventricular geometry, in these subjects.

METHODS

Participants

We studied 75 patients with histories of KD who were followed up as outpatients in Akita University Hospital. Seventeen patients had CAAs

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Abbreviations

Ao-ED = End-diastolic aortic dimension

Ao-ES = End-systolic aortic dimension

BP = Blood pressure

CAA = Coronary artery aneurysm

KD = Kawasaki disease

LVMI = Left ventricular mass index

PP = Pulse pressure

confirmed with coronary angiography (group A). Coronary arteries with diameters > 4 mm were considered CAAs. Fifty-eight patients had no signs of CAA on echocardiography (group B). In group B, 25 patients displayed transient coronary artery dilation during the acute stage of KD and subsequently had no dilated lesions during or after the convalescent stage. The other 33 patients in group B had no coronary artery lesions at any stage of the illness. KD was diagnosed in each patient on the basis of the guidelines at the time of illness. Of the 75 patients, 63 received intravenous immunoglobulin therapy during the acute stage of the illness, whereas nine did not. For three patients, information about administration of intravenous immunoglobulin was unavailable. Fifty-seven subjects were enrolled as controls. They presented symptoms or signs of suspected heart disease, and any disease was subsequently confirmed by examinations. None of the control subjects had histories of systemic disease, including KD. The institutional review board of the Akita University Faculty of Medicine approved this study, and informed consent was obtained from the participants and their parents.

Measurement of Central Aortic Elastic Properties

Trained physicians (J.O. and M.T.) performed echocardiography according to standardized protocols for a commercially available system (ProSound α10; Aloka, Tokyo, Japan). We retrospectively estimated the interventricular septal and posterior wall thicknesses and left ventricular end-systolic and end-diastolic dimensions by M-mode echocardiography from the parasternal short-axis view. These parameters were used to calculate left ventricular fractional shortening and left ventricular mass. End-systolic aortic dimension (Ao-ES) and end-diastolic aortic dimension (Ao-ED) were obtained by M-mode echocardiography from the parasternal long-axis view 2 to 3 cm above the aortic valve using the leading edge–to–leading edge technique according to the guidelines of the American Society of Echocardiography (Figure 1).[21] Ao-ES was measured at the time of the full opening of the aortic valve and Ao-ED at the peak of QRS complex by electrocardiography. Left ventricular end-diastolic dimension, left ventricular mass, Ao-ES, and Ao-ED were indexed according to body surface area. Each echocardiographic measurement was averaged over three consecutive cardiac cycles. Systolic and diastolic blood pressures (BPs) were measured in the right arm noninvasively in the supine position. Using these parameters, we calculated the aortic stiffness index, aortic distensibility, and aortic strain of the ascending aorta according to the following formulas[22-24]:

$$\text{aortic stiffness index} = \ln(\text{systolic BP}/\text{diastolic BP})/[(\text{Ao-ES} - \text{Ao-ED})/\text{Ao-ED}],$$

$$\text{aortic distensibility } (\text{cm}^2/\text{dyne}\cdot 10^{-4}) = [2 \times (\text{Ao-ES} - \text{Ao-ED})]/[\text{Ao-ED} \times (\text{systolic BP} - \text{diastolic BP})],$$

and

$$\text{aortic strain } (\%) = 100 \times (\text{Ao-ES} - \text{Ao-ED})/\text{Ao-ED}.$$

Statistical Analyses

Quantitative data are presented as mean ± SD and categorical data as percentages. To compare the differences in the characteristics between the two groups, Student's unpaired *t* test was used for parametric variables and the Mann-Whitney *U* test was used for nonparametric variables. Pearson's and Spearman's correlation analyses were used to assess possible relationships between the indices of aortic elastic properties and clinical characteristics, as appropriate. Furthermore, linear and curvilinear regression analyses were performed to assess the significant relationships between the variables, and the highest coefficient determination was retained. Because aortic elastic properties are reportedly influenced by age,[25] multivariate regression analysis was used to identify independent relevance, including age-related variables, to indices of aortic elastic properties in the patients with KD. *P* values <.05 were considered statistically significant. Statistical analyses were performed using SPSS version 17.0 for Windows (SPSS, Inc., Chicago, IL).

From the echocardiographic data, 10 random images were analyzed by two blinded observers (J.O. and M.T.) and by a single observer (J.O.) at two time points to assess interobserver and intraobserver differences, respectively, in Ao-ES and Ao-ED measurements. These differences were analyzed using Pearson's correlation analysis and the Bland-Altman technique.[26]

RESULTS

Clinical and Laboratory Characteristics of the Study Population

Table 1 shows the clinical and laboratory characteristics of the patients with KD and controls. No significant differences in age, body surface area, diastolic BP, indexed Ao-ES, indexed Ao-ED, indexed left ventricular end-diastolic dimension, or left ventricular fractional shortening were found between the two groups. Systolic BP, pulse pressure (PP), left ventricular mass index (LVMI), and aortic stiffness index in patients with KD were significantly greater than in controls. In contrast, aortic distensibility and aortic strain in patients with KD were significantly lower than those in controls. Although the KD group included significantly more male subjects, no significant gender differences in BP measurements or indices of aortic elastic properties were found between patients with KD and controls.

Relationships between the Indices of Aortic Elastic Properties and Clinical and Echocardiographic Characteristics

Patients with KD. Table 2 shows the clinical characteristics of groups A and B. Age at the time of study, male gender, febrile period, body surface area, PP, and aortic stiffness index in group A were significantly greater than in group B. In contrast, aortic distensibility and aortic strain in group A were significantly lower than in group B. In group B, no significant differences in clinical and echocardiographic characteristics were found between those with and those without histories of transient coronary artery dilation. Interestingly, subjects in group B had greater aortic stiffness indices and lower aortic distensibility and aortic strain compared with controls (Tables 1 and 2).

Table 3 shows the relationships between the indices of aortic elastic properties and clinical and echocardiographic characteristics in the