Arterial Hemodynamics in Patients After Kawasaki Disease

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Background—Histopathological findings in the acute stage of Kawasaki disease (KD) indicate widespread vascular inflammation that involves not only coronary arteries but also systemic arteries. This may cause changes in systemic arterial wall properties after KD, which could have adverse effects on arterial hemodynamics (an important predictor of cardiovascular morbidity and mortality).

Methods and Results—Systemic arterial hemodynamics were investigated by measuring aortic input impedance during cardiac catheterization in 42 KD patients who had developed coronary artery lesions (CALs) in the acute stage of KD. The KD patients were subdivided into 2 groups according to the angiographic findings (group 1A, 26 patients with persistent CALs; group 1B, 16 patients with regressed CALs), and results were compared with those of 36 referents (group 2). Compared with referents, characteristic impedance was significantly higher for KD patients (137.0±5.1, 125.7±8.2, and 97.9±4.1 dynes · cm⁻² · m² for group 1A, group 1B, and group 2, respectively), and total peripheral arterial compliance indexed to age-specific values was significantly lower for KD patients (group 1A 72.9±4.2% of normal; group 1B 70.6±5.9% of normal; group 2 97.7±4.0% of normal; for both variables, P<0.05 for each KD group versus group 2; P=NS between KD groups), which suggests that both central and peripheral arterial wall stiffness increased after KD regardless of persistence of CALs. Also, indices of arterial wave reflection (reflection coefficient, reflection factor, and augmentation index) were all significantly higher in KD patients than in referents (P<0.05), with the result that the aortic pressure waveforms of the present KD patients resembled those generally observed in the elderly. In addition, levels of circulating markers of endothelial dysfunction (ACE and von Willebrand factor) were associated with increased vascular stiffening in KD patients but not in referents.

Conclusions—These results indicating abnormal arterial hemodynamics after KD highlight the importance of regular monitoring of the systemic arterial bed and potentially relevant cardiovascular events in long-term follow-up of KD. (Circulation. 2005;111:2119-2125.)

Key Words: arteries • coronary disease • Fourier analysis • hemodynamics • risk factors

K

awasaki disease (KD) in children is an acute inflammatory syndrome that takes the form of systemic vasculitis.2–4 Coronary artery dilation and aneurysm formation occur in 10% to 15% of KD patients during its acute stage.2–4 Because morbidity and mortality late after resolution of acute KD appear to be associated primarily with coronary artery lesions (CALs),1,2,4 attention has been focused on the long-term outcome of CALs after acute KD; however, histopathologic findings in the acute stage of KD indicate widespread vascular inflammation with endothelial and medial degeneration and subsequent fibrous scar formation that involve systemic and coronary arteries.5,6 Furthermore, such abnormalities in the systemic vascular bed may persist for years after acute KD,6–8 possibly causing lasting changes in arterial hemodynamics, which are an important predictor of cardiovascular morbidity and mortality.9–11

Aortic input impedance integrates functional and structural changes in systemic vascular properties, providing comprehensive information about the state of the vascular bed that includes both frequency-independent static (resistance) and frequency-dependent dynamic (stiffness and wave reflection) components.12,13 In the present study, we examined aortic input impedance to test our hypothesis that arterial hemodynamics are abnormal after KD.

Methods

Patients

Cardiac catheterization was performed in 42 consecutive KD patients who had a history of KD at least 1 year before the study and who had developed CALs in the acute phase of KD. Coronary arteries with diameters of ≥4 mm, as indicated by 2D echocardiography, were considered to have CAL. The KD patients were subdivided into 2
groups on the basis of coronary angiographic findings: 26 patients with persistent CAL (group 1A) and 16 patients with regressed CAL (group 1B). On the basis of the “Guidelines for Coronary Lesions in Kawasaki Disease” reported by the Research Committee on Kawasaki Disease, angiographically normal coronary arteries were classified as regressed CAL, and other coronary arteries were classified as persistent CAL. Serial echocardiography showed that all 42 KD patients had a normal left ventricular shortening fraction and no evidence of valvular incompetence. Also, there was no overt systemic arterial disease (aneurysms/vasculitis) in any of the present patients. All KD patients were treated with intravenous administration of gamma globulin (400 mg · kg−1 · d−1 for 5 consecutive days) during the acute stage. Steroids were used in 3 group 1A patients and 2 group 1B patients, as decided by the attendant physician.

The referent group (group 2) consisted of 36 patients with small or closed ventricular septal defect (calculated pulmonary-to-systemic flow ratio = 1.0). All ventricular septal defects in referent subjects were subpulmonic, which can cause aortic valve prolapse and resultant aortic regurgitation.14 Accordingly, cardiac catheterization was performed for these patients to examine deformity of aortic valves and aortic regurgitation. There was no significant regurgitation in any of the referent subjects examined. Written informed consent was obtained from the parents of all patients, and the procedures were approved by the Saitama Medical School Committee on Clinical Investigation.

Procedures
During routine cardiac catheterization, ascending aortic pressure and flow were measured simultaneously with a high-fidelity pressure transducer and a catheter-mounted flow-velocity probe (Miller Instruments, Inc). The catheter was advanced retrogradely across the aortic valve to help stabilize it and to keep the sensor in the center of the stream. The maximum ascending aortic cross-sectional area was obtained from 2D transthoracic echocardiograms at the time of the catheterization and was used to convert flow velocity to volume flow. Previous reports have confirmed the validity of this method for measurement of instantaneous aortic volume flow.13,15 Data were digitalized at 500 Hz on a personal computer and stored for subsequent offline analysis.

Blood samples taken at the level of the inferior vena cava were obtained via the catheter and were centrifuged. Serum levels of ACE and plasma levels of von Willebrand factor (vWF) were measured as markers of endothelial function/damage16,17 with previously reported methods.18,19 Interassay and intra-assay variation was <8% for these measurements.

Data Analysis
Two to five consecutive steady-state beats during expiration were signal averaged and used for impedance analyses. Cardiac output derived from ascending aortic volume flow was indexed to body surface area (cardiac index). Impedance moduli were computed from Fourier components of pressure and flow data.20,21 Total vascular resistance was calculated by subtracting mean right atrial pressure from mean ascending aortic pressure and dividing the difference by cardiac index. Characteristic impedance (Zc), a measure of proximal arterial stiffness, was calculated by averaging all impedance moduli between 2 and 10 Hz. Arterial compliance (C) was calculated by the method reported by Liu et al.,22 as follows: C = SVI/K(Ps – Pd), where SVI is stroke volume index, Ps is aortic pressure at incisura, Pd is diastolic aortic pressure, and K is an area index obtained by dividing the total area under the aortic pressure curve by the diastolic area. As previously reported, arterial compliance is influenced by body size (body surface area [BSA]), and arterial compliance indexed to BSA changes nonlinearly with age and is predicted by the equation C/BSA = 1.34 + 1.62 · e−0.12 · age.23 Therefore, calculated values of C/BSA were indexed to these age-specific predicted values and expressed as percentage of the predicted values.

Data on wave reflections were obtained by resolving the measured pressure and flow waveforms into their forward and reflected components, as previously described.24 Reflection coefficient was calculated as the ratio between peak amplitude of forward and backward pressure.25 Reflection index, which indicates the degree of wave reflection, was defined as the amplitude of oscillation of impedance moduli about the Zc and was estimated as Zmax-Zmin)/Zc, where Zmin and Zmax are the values of minimum and maximum input impedance moduli.25 Augmentation index was calculated as a time-domain estimate of the contribution of the reflections relative to the pulse pressure.25,26 The inflection point on the upstroke or down stroke of the pressure wave was identified from the first local minimum of the first derivative of the signal as reported previously.26,27

Statistical Analysis
All values were expressed as mean±SEM. Comparisons of mean values among the 3 groups were performed by ANOVA. When ANOVA yielded probability values <0.05, multiple comparisons were made with Bonferroni adjustment. The effect of age on measurements of vascular stiffness (characteristic impedance and arterial compliance) was taken into account with multivariable regression analysis with age and group included as independent variables. ANCOVA was used to test for differences in age-associated change in vascular stiffness among the 3 groups. A probability value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed with Systat version 6.0.

Results
Table 1 summarizes the patient characteristics of each group. Group 1A and Group 1B had similar durations of febrile periods. Because group 1A contained patients who had undergone 1 or 2 previous catheterizations for follow-up of...
TABLE 2. Hemodynamic and Impedance Data

<table>
<thead>
<tr>
<th>Hemodynamics</th>
<th>Group 1A</th>
<th>Group 1B</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>108.1±3.5</td>
<td>110.7±3.9</td>
<td>107.5±3.1</td>
</tr>
<tr>
<td>Cardiac index, L·min⁻¹·m⁻²</td>
<td>4.3±0.2</td>
<td>4.2±0.2</td>
<td>4.6±0.1</td>
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<tr>
<td>Systolic AOP, mm Hg</td>
<td>98.8±2.7</td>
<td>94.7±3.6</td>
<td>97.8±2.2</td>
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<tr>
<td>Diastolic AOP, mm Hg</td>
<td>69.6±2.5</td>
<td>64.2±3.4</td>
<td>66.1±1.8</td>
</tr>
<tr>
<td>Mean AOP, mm Hg</td>
<td>84.7±5.1</td>
<td>80.3±3.5</td>
<td>82.3±1.9</td>
</tr>
<tr>
<td>Impedance data</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Rt, dyne·s·cm⁻³·m⁻²</td>
<td>1641.7±96.7</td>
<td>1504.4±84.2</td>
<td>1420.6±46.1</td>
</tr>
<tr>
<td>Zc, dyne·s·cm⁻³·m⁻²</td>
<td>137.0±5.1</td>
<td>125.7±6.2</td>
<td>97.9±4.1</td>
</tr>
<tr>
<td>C, mL·mm Hg⁻¹·m⁻²</td>
<td>1.17±0.09</td>
<td>0.94±0.09</td>
<td>1.24±0.09</td>
</tr>
<tr>
<td>C/BSA, % of normal</td>
<td>72.9±4.2</td>
<td>70.6±5.9</td>
<td>97.7±4.0</td>
</tr>
<tr>
<td>Wave reflection</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Reflection coefficient</td>
<td>0.19±0.01*</td>
<td>0.18±0.01</td>
<td>0.11±0.01</td>
</tr>
<tr>
<td>Reflection index</td>
<td>0.68±0.06</td>
<td>0.67±0.06</td>
<td>0.30±0.02</td>
</tr>
<tr>
<td>Augmentation index</td>
<td>0.19±0.03*</td>
<td>0.18±0.04*</td>
<td>0.09±0.01</td>
</tr>
</tbody>
</table>

*Significant differences were observed between group 1A and group 2 and between group 1B and group 2; no significant differences were observed between KD groups.

In initial analysis, the C value was lower for KD patients than for referents, but the difference was not statistically significant; however, in multivariable analysis with age included as an independent variable, the C values of each KD group were significantly lower than those of the referents (P<0.05). There was no significant difference between groups 1A and 1B. These results are consistent with the finding that C/BSA was significantly lower in groups 1A and B than in group 2 (72.9%, 70.6%, and 97.7% of normal value, respectively). Thus, total peripheral arterial stiffness also increased after KD.

To further test whether stiffening of the proximal arteries parallels the stiffening of peripheral arteries, we examined the correlation between characteristic impedance and arterial compliance. There was no significant correlation between these 2 variables, which indicates that progression of arterial stiffening differs between central and proximal arteries.

Wave Reflection
Indices of wave reflection for each group are shown in Table 2. Values of reflection coefficient, reflection index, and augmentation index were significantly higher for KD patients (with or without CAL) than for referents, which indicates an increase in arterial wave reflection after KD. Panel A of the Figure shows forward, backward, and measured pressure waveforms of representative patients from each group. A marked reflected wave (dashed line) was observed in both KD patient groups, whereas there was minimal reflection in the referent patient. Note that the measured pressure wave contour differed considerably between the KD patients and the referent subject. In the KD patients, peak systolic pressure occurred in late systole after the inflection point, resulting in greater augmentation index, whereas in the referent patient, peak systolic pressure preceded the inflection point, resulting in lower augmentation index. Panel B of the Figure shows the input impedance spectra of the patients presented in panel A. In the KD patients, there was marked oscillation about the characteristic impedance, which is consistent with increased reflection index and thus an increased degree of wave reflection. In contrast, the impedance spectrum of the referent patient loses its oscillatory character and becomes extremely flat (i.e., equal to characteristic impedance), which indicates less wave reflection.

Circulating Markers of Endothelial Function/Damage
Table 3 shows circulating levels of ACE and vWF of each group. There was no significant difference in levels of ACE or vWF among the 3 groups. For KD patients, when age was taken into account, there was a significant negative correlation between ACE levels and characteristic impedance, a significant positive correlation between ACE levels and arterial compliance, and a significant positive correlation between vWF levels and characteristic impedance (Zc=3.99×age−3.95×ACE+148.6; C=0.044×age+0.038×ACE+0.71; Zc=3.38×age+0.37×vWF+61.6; P<0.01 for all coefficients); no such correlations were observed in the referent group. Although ACE and vWF were not independently associated with characteristic impedance or arterial compliance, owing to correlation between ACE and vWF (r=0.59, P<0.05), persistent CAL, mean age and the interval from initial onset of KD were higher in group 1A than in group 1B, but the difference was not statistically significant (unpaired t test). All KD patients were receiving antiplatelet doses of aspirin, and 11 KD patients were receiving warfarin and aspirin.

Hemodynamics and Impedance Data
Table 2 shows hemodynamic and impedance data of each group. The 3 groups had similar mean values of heart rate and blood pressure. Cardiac index was lower for KD patients than for the referent group, and total vascular resistance was higher for KD patients than for the referent group, but these differences were not statistically significant (both P>0.05). Characteristic impedance (Zc) was significantly higher in KD patients than in referents (P<0.01), which indicates an increase in stiffness of proximal arteries after KD. Because characteristic impedance of children may be influenced by age (as has been observed in adults), we first examined the relationship between age and characteristic impedance in the referent group and found a significant positive correlation (Zc=2.6×age+83.5, r=0.53, P<0.01). Therefore, multivariable analysis was performed with age and group included as independent variables. We found a significant positive correlation between characteristic impedance and age (P<0.005 for coefficient) and found significant differences in characteristic impedance among the groups (P<0.05). Post hoc analysis revealed a significant difference between each KD group and the referent group (P<0.05) but not between the 2 KD groups. Thus, proximal arterial stiffness increased after KD with or without CAL.
these results suggest a close association between endothelial dysfunction and vascular stiffening after KD.

**Discussion**

This report presents novel findings with regard to alteration of systemic vascular properties late after KD. We found that both central and peripheral arterial wall stiffness, represented by characteristic impedance and arterial compliance, increased significantly after KD, but we also found a difference in the degree of stiffening between the 2 arterial beds. These changes in KD patients were concurrent with increased wave reflection, which can adversely affect ventricular-vascular interaction.28 Notably, these changes in arterial wall stiffness and wave reflection were observed even in patients whose CALs had morphologically (angiographically) regressed. Also, levels of circulating markers of endothelial dysfunction were associated with increased vascular stiffening after KD. These results highlight the importance of regular monitoring of the systemic arterial bed and potentially relevant cardiovascular events in long-term follow-up of KD.

**Arterial Stiffening After KD**

Characteristic impedance and arterial compliance are useful measures of the elastic properties of the arterial wall.12,26 In adults, these variables are affected by age-related functional and structural changes in the arterial wall.29,30 We recently reported age-associated changes in arterial compliance in normal children.23 In the present study, we showed for the first time that in children, characteristic impedance increases with increasing age. When this age effect on arterial properties is taken into account, the present findings clearly demonstrate increased characteristic impedance and decreased arterial compliance late after KD. Importantly, these changes in arterial wall properties were observed not only in patients with persistent CAL but also in patients whose CAL had regressed. Characteristic impedance represents stiffness of the proximal arterial bed, whereas arterial compliance represents stiffness of more distal parts of the arterial system.28 Thus, the changes in these variables in the present study indicate that both proximal and peripheral arterial stiffness are increased in KD patients late after resolution of acute inflammation.

The present results are partially consistent with those of previous studies of vascular stiffness after KD in specific arterial beds. Noto et al31 showed increased carotid arterial stiffness in 20 KD patients with CAL using a stiffness index based on ultrasonographic measurements. Cheung et al32 observed increased pulse-wave velocity (a measure of arterial stiffness) in the brachial arterial system of KD patients with and without CAL. The present data demonstrate several novel aspects of systemic arterial stiffening after KD. First, we found that arterial stiffness is increased throughout the entire arterial system, which includes both the central and total peripheral arterial beds. In addition, the extent of such change differed considerably between the central and peripheral arterial beds.

**Increased Wave Reflection After KD**

The present findings of increased wave reflection and resultant changes in aortic pressure contour are consistent with the present findings of changes in characteristic impedance and arterial compliance. The magnitude and incidence of wave
reflection are related to the geometry of the arterial system: Reflection is increased by augmentation of impedance mismatch of the vascular tree.\(^{26,28}\) In systems without impedance mismatch, input impedance is equal to characteristic impedance.\(^{28}\) Therefore, an increase in deviation of impedance spectra from characteristic impedance in KD patients (as indicated by increased reflection index) indicates an increase in impedance mismatch and thus increased variation in regional vascular properties or loss of homogeneity of the arterial bed, which results in increased wave reflection.

Such a profile of wave reflection indicates alteration of the pressure waveform at the ascending aorta, which is consistent with the marked increase in augmentation index in the present KD patients compared with referents (Figure 1). Murog et al\(^{25}\) classified aortic pressure waveform into 3 types: type A, in which peak systolic pressure occurs in late systole after an inflection point with augmented wave reflection; type C, in which peak systolic pressure precedes an inflection point with minimal wave reflection; and type B, a transitional waveform between type A and type C. They and others have reported that the type A pressure contour primarily occurs in elderly subjects, whereas nearly all adults under the age of 30 years exhibit type C.\(^{25,27}\) It is interesting that children who have had KD exhibit a pressure contour similar to the type that is most common in elderly subjects, and this similarity further highlights the extent of abnormality in the systemic vascular bed after KD.

**Implications of Changes in Arterial Hemodynamics After KD**

Arterial hemodynamic indices reflect both structural and functional properties of the arterial wall.\(^{28}\) Histopathologic studies have demonstrated destruction of the coronary arterial wall during the acute phase of KD.\(^{6,7,33}\) Infiltration by inflammatory cells begins in the intima with degradation of endothelial cells and disruption of the elastic lamina. These changes then spread to the media and adventitia. In the subsequent reparative process, elastic tissue is replaced by fibrous scar tissue, and intimal thickening and proliferation of medial smooth muscle cells are sometimes observed in the convalescent stage.\(^{6,7,33}\) Importantly, similar histopathologic changes have been observed in systemic arteries ranging from large elastic and musculoelastic arteries to small intravisceral arteries.\(^{7,8,34}\) Furthermore, intimal thickening with fibrous scar formation and smooth muscle proliferation have been observed in systemic arteries of children who have had KD, even years after resolution of acute illness.\(^{6–8,35,36}\) Thus, structural abnormalities that result from the reparative process after acute vasculitis may persist in systemic arteries after KD and may contribute to the increase in vascular wall stiffness.

In addition to structural changes in the arterial wall, dynamic control of vascular tone may contribute to the changes in arterial hemodynamics in KD. Vascular endothelium plays an important role in the regulation of vascular tone.\(^{37,38}\) The endothelium synthesizes vWF,\(^{15,38,39}\) and increased levels of circulating vWF have been found in several vascular diseases, including peripheral,\(^{39}\) cerebral,\(^{40}\) and coronary artery disease.\(^{41}\) High levels of vWF are also associated with increased risk of cardiovascular mortality.\(^{39,41}\) Consequently, it has been proposed recently that the level of circulating vWF could be useful as a marker of generalized endothelial dysfunction.\(^{38,39}\) The endothelium also makes a large contribution to the levels of circulating ACE,\(^{42,43}\) and decreased ACE levels have been observed in association with endothelial injury both in vitro and in vivo.\(^{34,43}\) Although there was no significant difference in mean levels of vWF or ACE between the present KD patients and referent subjects, significant correlation was observed between the measures of arterial stiffness and both vWF and ACE. Dhillon et al\(^{44}\) observed impaired endothelial function years after KD, as indicated by abnormal endothelium-dependent vasodilatation after reactive hyperemia of the brachial artery. Their data and ours suggest that in addition to the potential contributions of vascular structural changes, endothelial dysfunction is at least partly responsible for the increased arterial stiffness observed after KD. Further studies of direct measurement of endothelial function combined with measurement of mechanical arterial function are needed to clarify the association between endothelial dysfunction and vascular stiffening after KD.

**Clinical Implications**

Arterial stiffness directly influences left ventricular afterload and coronary perfusion,\(^{12,27,28}\) and it also appears to approximately parallel the extent of atherosclerosis.\(^{45}\) Arterial stiffening may be sufficient on its own to cause endothelial dysfunction.\(^{46}\) In addition, in recent longitudinal studies of several diseases and conditions, arterial stiffness has been shown to be an independent predictor of cardiovascular morbidity and mortality, including strokes, abdominal aortic aneurysm, peripheral artery disease, heart failure, and coronary heart disease.\(^{9–11,47–49}\) Thus, the present results indicating increased arterial stiffness after KD are further evidence of the need for long-term follow-up of KD patients (regardless of persistence of CAL) for cardiovascular complications, including conditions other than coronary artery disease. Also, the present results indicate the need for prospective studies to assess the potential benefits of early therapeutic intervention aimed at improving abnormal arterial hemodynamics and thereby reducing the risk of cardiovascular events.

**Study Limitations**

Although it has been reported that aspirin does not affect levels of vWF,\(^{13}\) administration of aspirin to KD patients can have effects on circulating indices of endothelial function and invasive hemodynamic measurements; however, doses of aspirin that have antiplatelet effects can improve vascular endothelial function\(^{50}\) and thus can improve arterial hemodynamics. Therefore, it is unlikely that the increased vascular stiffening and associated changes in circulating indices of endothelial function in KD patients observed in the present study are due to the use of aspirin.

Although the present results show no difference in the degree of vascular stiffening between the 2 KD groups, the numbers of patients in the present study groups were relatively small. The effect sizes of characteristic impedance and C/BSA calculated in the present study were 42 dyne · s · cm\(^{-5}\) · m\(^2\) and 22%, respectively. Therefore, we cannot exclude the
This article was retracted in June 2012.

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An erratum has been published regarding this article. Please see the attached page for:
/content/125/23/e1020.full.pdf
The four articles listed below have been retracted due to ethical violations. The corresponding author’s institution, Saitama Medical University, reported to the editors of Circulation, that Dr. Hideaki Senzaki did not receive approval for these studies from the institutional internal ethics committee. Furthermore, in each of the articles referenced below, it was determined that Dr. Senzaki misinformed the editors and readers of Circulation by stating that the studies had received the necessary approval from his institutional review board.


