Novel and Traditional Cardiovascular Risk Factors in Children After Kawasaki Disease
Implications for Premature Atherosclerosis

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OBJECTIVES
We determined the profile of cardiovascular risk factors in children late after Kawasaki disease (KD) and compared it with that of age-matched healthy children.

BACKGROUND
Concerns have been raised regarding the possibility of a predisposition of KD to premature atherosclerosis later in life.

METHODS
A cohort of 102 subjects were studied: 37 KD patients with coronary aneurysms (group I), 29 KD patients with normal coronary arteries (group II), and 36 healthy age-matched children (group III). The fasting total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, apolipoprotein (apo) A-I, apoB, and homocysteine levels were compared among the three groups. In addition, blood pressure and brachioradial arterial stiffness, as determined by pulse wave velocity (PWV), were measured and compared.

RESULTS
Group I subjects had lower HDL cholesterol (p = 0.016) and apoA-I levels (p = 0.044) and higher apoB levels (p = 0.029) and PWV (p = 0.001) than group III control subjects. Likewise, the apoB levels (p = 0.007) and PWV (p = 0.042) were higher in group II than in III subjects, although their HDL cholesterol (p = 0.54) and apoA-I (p = 0.52) levels were similar. The LDL cholesterol levels were higher in group I and II patients than in controls, although not statistically significant (p = 0.17). Blood pressure and homocysteine levels did not differ among the groups.

CONCLUSIONS
An adverse cardiovascular risk profile, as characterized by a proatherogenic alteration of the lipid profile and increased arterial stiffness, occurs in children after KD. The profile is worse in those with than in those without coronary aneurysms. (J Am Coll Cardiol 2004;43:120–4) © 2004 by the American College of Cardiology Foundation

It has now been more than 25 years since the first description of Kawasaki disease (KD) (1). Concerns have been raised regarding the possibility of its predisposition to premature atherosclerosis in adulthood (2–6). Nonetheless, data on the cardiovascular risk profile long after resolution of the acute phase of KD remain limited and, in some aspects, controversial (6–9).

Alteration of the lipid profile during acute-phase KD, with a decrease in total cholesterol, high-density lipoprotein (HDL) cholesterol and apolipoprotein (apo) A-I levels, has been well documented (8–10). Nonetheless, whether such alterations persist after resolution of the acute inflammation is controversial (8–10). Furthermore, data on low-density lipoprotein (LDL) cholesterol and apo concentrations late after the acute illness are not available.

A number of novel cardiovascular risk factors have recently been described in adults. Arterial stiffness has recently been shown to be an independent predictor of cardiovascular morbidity and mortality in adult patients with hypertension (11) and end-stage renal disease (12). Increased coronary (13) and carotid (14) arterial stiffness has been documented in KD patients with coronary aneurysms. However, whether stiffness of peripheral conduit arteries is likewise altered in those with and without aneurysms remains unknown. More importantly, the interplay between arterial stiffness and other cardiovascular risk factors has hitherto not been explored. An elevated homocysteine level has also been demonstrated to be an independent risk factor for atherosclerosis in adults (15). Reduced methylenetetrahydrofolate reductase (MTHFR) activity, among other determinants, is associated with a moderately elevated homocysteine level (16). Although MTHFR gene polymorphism has been implicated in a predisposition to coronary aneurysm formation in children with KD (17), the plasma homocysteine levels in these patients are unknown.

In this study, we determined the profile of novel and traditional cardiovascular risk factors in KD patients late after resolution of the acute illness and compared the findings with those of age-matched healthy children. We further determined the inter-relationships between blood pressure (BP), lipid and homocysteine levels, and peripheral conduit arterial stiffness.

METHODS
Subjects. Patients with history of KD were recruited from the pediatric cardiac clinic of Grantham Hospital. All of the
recruited patients had a normal left ventricular shortening fraction and absence of valvar incompetence, as documented by serial echocardiographic studies. Patients diagnosed as having KD within 12 months of the study were excluded to minimize a potential confounding influence relating to subacute inflammation (18). Healthy age-matched subjects were recruited as control subjects. These were healthy children previously discharged from our clinic with a diagnosis of a functional heart murmur and their healthy siblings. The institutional ethics committee approved the study, and the parents of all subjects gave written, informed consent.

The subjects attended for the study after an overnight fast. Body weight and height were measured, and body mass index was calculated accordingly. All subjects rested for at least 15 min before BP and vascular assessments. Blood pressure in the right arm was measured twice using an automatic oscillometric device (Dinamap, Critikon Inc., Tampa, Florida), with the subjects in the seated position, and the average of the two readings was taken. Assessment of peripheral conduit arterial stiffness and blood withdrawal was then performed sequentially, as described subsequently.

From the medical records, the following patient data were retrieved: interval from disease onset to time of study, coronary complications, cardiac symptoms, and medications at the time of study. Coronary aneurysms were documented by serial two-dimensional echocardiography. Based on the patients’ status and the presence or absence of coronary complications, the cohort was categorized into three groups for comparisons. Group I comprised patients with coronary aneurysms, whether persistent or regressed; group II comprised patients without coronary complications; and group III comprised healthy control subjects.

**Measurement of arterial stiffness.** Stiffness of the brachio-radial arterial segment was assessed by measuring the pulse wave velocity (PWV), with the subjects lying supine. Pulse wave velocity is related to the square root of elastic modulus, according to the Moens-Korteweg equation (19). Hence, the stiffer the artery, the faster the PWV. A previously validated photoplethysmographic technique (20) was used to measure the transit time required for the pulse to travel from the brachial artery at the elbow to the radial artery at the wrist. The transit time was determined from the time delay between the foot of the corresponding brachial and radial pulse waves. The average of three readings was taken. Pulse wave velocity was calculated by dividing the distance between the two points by transit time. Intraobserver variability for measurement of PWV, as determined from the mean and SD of the differences in two consecutive results from 20 studies, was 0.08 ± 0.82 m/s.

**Blood investigations.** Venous blood was withdrawn for measurement of fasting total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, apoA-I, apoB, and total plasma homocysteine levels. Plasma total cholesterol level was determined enzymatically using a Hitachi 912 analyzer (Roche Diagnostics, GmbH, Mannheim, Germany). The HDL cholesterol was measured using a homogeneous method with polyethylene glycol-modified enzymes and sulphated alpha-cyclodextrin. The LDL cholesterol was calculated by the Friedewald equation. Levels of apoA-I and apo B were determined by rate nephelometric assays on the Image analyzer (Beckman Coulter Inc., Fullerton, California). Total plasma homocysteine was measured by the AxSYM homocysteine assay (Abbott Laboratories Inc., Abbott Park, Illinois), based on the fluorescence polarization immunoassay technology.

**Data analysis.** Data are presented as the mean ± SD, unless otherwise stated. To compare differences in variables among the three groups, one-way analysis of variance (ANOVA) was performed. When values of p < 0.05 were yielded by ANOVA, multiple comparisons between two groups by the unpaired Student t test were performed. All of the p values are presented, and no correction was made for the multiple tests. For categorical variables, the chi-square test was performed. Pearson correlation analysis was used to assess the correlation between brachioradial PWV and other cardiovascular risk factors. Stepwise multiple linear regression was used to identify significant determinants of brachioradial PWV. A value of p < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 10.0 (SPSS Inc., Chicago, Illinois).

**RESULTS**

**Subjects.** A total of 102 subjects were studied. All of the subjects were Chinese in origin. Group I comprised 37 patients, 21 of whom had persistent coronary aneurysms, whereas 16 had aneurysms that had regressed. Group II comprised 29 patients who did not have coronary complications. Of the total of 66 patients with KD, all but 5 patients had received intravenous immunoglobulin therapy during the acute phase of the illness, and 32 patients were maintained on long-term aspirin therapy. Group I patients were studied at 7.8 ± 3.7 years after KD, whereas group II patients were studied at 6.2 ± 2.4 years since the illness (p = 0.08). None were symptomatic and none required coronary artery interventions. Group III comprised 36 healthy control subjects. The demographic and hemodynamic data of the three groups are summarized in Table 1. There were no significant differences in age, gender distri-
Correlation between LDL cholesterol and apoB levels (r = 0.001) was significantly stronger in group I subjects than in controls. There was a similarly strong correlation between HDL cholesterol and apoA-I levels (r = 0.001) in group I and II subjects than in group III subjects. The apoA-I level was likewise significantly lower in group I subjects (Fig. 1) than in both group II (p = 0.016) and III (p = 0.001) subjects. This resulted in an increased ratio of total cholesterol to HDL cholesterol in group I subjects. The apoA-I level was likewise significantly lower in group I and II subjects than in controls (Table 2), the differences were not statistically significant (p = 0.001).

The apoB levels, on the other hand, were significantly higher in group I (p = 0.029) and group II (p = 0.007) subjects than in controls. There was a similarly strong correlation between LDL cholesterol and apoB levels (r = 0.63, p < 0.001). However, although LDL cholesterol levels appeared higher in group I and II subjects than in controls (Table 2), the differences were not statistically significant. No statistically significant differences in total cholesterol (p = 0.78) and triglyceride levels (p = 0.07) were found among the three groups.

Homocysteine level. The serum homocysteine levels in group I, II, and III subjects were 6.16 ± 2.41 μmol/l, 5.63 ± 1.98 μmol/l, and 5.76 ± 1.64 μmol/l, respectively. The differences among the groups were not significant (p = 0.55).

Arterial stiffness. The PWV of group I subjects (7.17 ± 1.79 m/s) was significantly higher than that of control subjects (5.89 ± 1.35 m/s, p = 0.001). Likewise, compared with controls, the PWV of group II subjects was significantly higher (6.71 ± 1.82 m/s, p = 0.042). There was, however, no significant difference in PWV between group I and group II subjects (p = 0.32) (Fig. 2).

For the entire cohort, PWV correlated with age (r = 0.29, p = 0.003), height (r = 0.28, p = 0.004), systolic BP (r = 0.29, p = 0.003), diastolic BP (r = 0.23, p = 0.021), homocysteine level (r = 0.343, p < 0.001), and LDL cholesterol level (r = 0.198, p = 0.047). In patients, PWV correlated with the duration since the onset of KD (r = 0.30, p = 0.032).

Multiple linear regression analysis of the entire cohort was used to identify significant determinants of PWV. The dependent variables included age, gender, height, weight, subject grouping, systolic and diastolic BPs, and homocysteine, HDL cholesterol, LDL cholesterol, apoA-I, apoB, and triglyceride levels. Significant determinants were subject grouping (beta = −0.23, p = 0.014), diastolic BP (beta = 0.22, p = 0.018), homocysteine level (beta = 0.29, p = 0.002), and LDL cholesterol level (beta = 0.19, p = 0.041, model R² = 0.26). When only the patient cohort (groups I and II) was analyzed, with the addition of duration since the onset of KD as a covariate into the multivariate model, only LDL cholesterol level was found to be significant (beta = 0.83, p = 0.011, model R² = 0.26).

**DISCUSSION**

This study demonstrates that children with a history of KD have an adverse cardiovascular risk profile long after resolution of the acute inflammatory illness. In those with coronary aneurysms, the profile is characterized by low HDL cholesterol and apoA-I levels, high apoB levels, and increased peripheral conduit arterial stiffness. In those without coronary complications, apoB levels and brachio-radial arterial stiffness are likewise increased. Although the LDL cholesterol levels are higher in patients than in

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**Table 1.** Demographic Data and Blood Pressure of Subjects in the Three Groups

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 37)</th>
<th>Group II (n = 29)</th>
<th>Group III (n = 36)</th>
<th>p Value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>9.0 ± 3.1</td>
<td>8.9 ± 3.2</td>
<td>9.1 ± 2.6</td>
<td>0.96</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>23/14</td>
<td>20/9</td>
<td>24/12</td>
<td>0.84</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>16.9 ± 2.7</td>
<td>16.0 ± 2.7</td>
<td>16.9 ± 3.4</td>
<td>0.37</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>108 ± 14</td>
<td>107 ± 8</td>
<td>108 ± 11</td>
<td>0.85</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>58 ± 9</td>
<td>58 ± 5</td>
<td>57 ± 8</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Data are presented as the mean ± SD. ANOVA = analysis of variance; BMI = body mass index; DBP = diastolic blood pressure; SBP = systolic blood pressure.

**Table 2.** Cholesterol and Apolipoprotein Levels of Subjects in the Three Groups

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 37)</th>
<th>Group II (n = 29)</th>
<th>Group III (n = 36)</th>
<th>p Value (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.38 ± 0.85</td>
<td>4.42 ± 0.82</td>
<td>4.28 ± 0.75</td>
<td>0.78</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.34 ± 0.26</td>
<td>1.46 ± 0.25</td>
<td>1.51 ± 0.33</td>
<td>0.037*</td>
</tr>
<tr>
<td>Total cholesterol/HDL cholesterol ratio</td>
<td>3.37 ± 0.80</td>
<td>3.03 ± 0.57</td>
<td>2.92 ± 0.61</td>
<td>0.016*</td>
</tr>
<tr>
<td>ApoA-I (g/l)</td>
<td>1.22 ± 0.21</td>
<td>1.34 ± 0.19</td>
<td>1.32 ± 0.17</td>
<td>0.026*</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/l)</td>
<td>2.65 ± 0.74</td>
<td>2.64 ± 0.73</td>
<td>2.37 ± 0.67</td>
<td>0.17</td>
</tr>
<tr>
<td>ApoB (g/l)</td>
<td>0.75 ± 0.22</td>
<td>0.81 ± 0.28</td>
<td>0.65 ± 0.16</td>
<td>0.022*</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>0.86 ± 0.34</td>
<td>0.70 ± 0.27</td>
<td>0.88 ± 0.37</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*Statistically significant. Data are presented as the mean ± SD. ANOVA = analysis of variance; Apo = apolipoprotein; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
controls, the difference did not reach statistical significance. In addition, we did not find any significant differences in total plasma homocysteine levels and systemic BP between patients and controls.

Lipid abnormalities in the acute phase of KD, with decreased total cholesterol, HDL cholesterol, and apoA-I levels, are reminiscent of those in acute infection and inflammation (8–10,21). Although several studies have suggested that such changes are transient (9,10), Newburger et al. (8) have reported that HDL cholesterol levels remain low as long as three years after the initial illness. The findings of the present study, performed at a mean of 7.1 years after the initial illness, agree with those of Newburger et al. (8) and further clarify that low HDL cholesterol levels are confined to patients with coronary aneurysm formation. As the severity of vasculitis in the acute phase is, to some extent, reflected by development of coronary lesions (22), our findings suggest that the degree of inflammation in the acute phase may have important bearings on late lipid abnormalities. Additionally, we have demonstrated low apoA-I levels in patient subgroup, a consistent finding, as apoA-I is the major protein constituent of plasma HDL. This might have important implications, however, because apoA-I, to a large extent, sets the plasma HDL levels (23) and is demonstrated to be antiatherogenic in transgenic mouse models (24). Besides apoA-I abnormalities, we have demonstrated significantly higher apoB levels in KD patients, more so in those with coronary aneurysms, a finding that has not been reported before. The finding that LDL levels do not differ significantly among the groups does not abrogate the overall adverse lipid profile in the KD groups, as apoB reflects the abundance of all the atherogenic lipoprotein particles—namely, LDL, intermediate-density lipoprotein, very-low-density lipoprotein, and lipoprotein(a). Indeed, apoB has been regarded as a better indicator of the attendant risk of coronary artery disease than LDL cholesterol in adults (25,26). To our knowledge, this is the first study to assess apo levels long term after KD.

The changes in cholesterol and lipoprotein levels long term after KD mimic those proposed to be atherogenic. Nonetheless, the underlying mechanisms remain speculative. Endothelial dysfunction has been shown years after resolution of the acute illness (7). Diminished lipoprotein lipase activity with reduced generation of HDL cholesterol, as a result of endothelial dysfunction, has been proposed as a possible mechanism (8). Furthermore, inhibition of lipoprotein lipase may decrease apoA-I levels by increasing its catabolism (27). The cause for the higher apoB and LDL cholesterol levels is unknown. Nonetheless, increased LDL cholesterol levels have been described in adults with chronic inflammation due to rheumatoid arthritis (28). Indeed, there is increasing evidence that low-grade vasculitis continues unabated after the end of the acute phase of KD (29). The changes in the lipid profile in our cohort may hence be a reflection of such a continued low-grade inflammatory process.

In addition to demonstrating a proatherogenic lipid profile, we have shown that KD patients, including those without coronary complications, have an increased brachioradial PWV and hence peripheral conduit arterial stiffness. This supplements the findings of those of Noto et al. (14), who demonstrated increased carotid arterial stiffness, using a stiffness index that relates systemic BP to a pulsatile change in carotid artery diameter, only in patients with coronary aneurysms. It is possible that diffuse vasculitis in the acute phase and the subsequent reparative process may lead to replacement of elastic tissue by fibrous scar (30), resulting in changes in the arterial wall structure and hence its elastic modulus. Endothelial dysfunction after KD (7) is probably also contributory in light of the crucial role of the endothelium in the regulation of vascular tone.

Pulse wave velocity is directly related to characteristic...
impedance (19). Importantly, the ascending aortic input impedance, which represents the hydraulic load presented by the systemic circulation to the left ventricle, is the composite of the impedance spectra of vascular beds perfused by the ascending aorta (19). Hence, an increase in characteristic impedance in the peripheral conduit artery may contribute to an increase in this hydraulic load. Furthermore, the increase in arterial stiffness may contribute to the pathogenesis of hypertension (31). In the present study, however, we did not find any difference in systemic BP between patients and controls. In contrast, Silva et al. (6) reported a higher systolic and diastolic BP in patients studied at 11 years after KD. Nonetheless, the oscillometric BP readings in their subjects were converted to z scores using normative data that were obtained by the auscultatory method. Given that oscillometric readings were higher than readings obtained by auscultation (32), their results should be interpreted with caution.

Conclusions. An adverse cardiovascular profile, as characterized by a proatherogenic alteration of the lipid profile and increased arterial stiffness, occurs in patients after KD. The profile is worse in patients with than in those without coronary aneurysms. Regular monitoring of these cardiovascular risk factors is hence warranted in the long-term follow-up of these patients.

REFERENCES