**Effects of Statin Therapy in Children Complicated With Coronary Arterial Abnormality Late After Kawasaki Disease**

--- A Pilot Study ---

Shih-Ming Huang, MD*,**,†‡,¶; Ken-Pen Weng, MD*,†‡,¶; Jeng-Sheng Chang, MD††; Wei-Yang Lee, MD**; Shih-Hui Huang, MS‡; Kai-Sheng Hsieh, MD*

**Background**  Ongoing low-grade inflammation and endothelial dysfunction persist in patients late after Kawasaki disease (KD). Statins not only reduce cholesterol, but also improve surrogate markers of atherosclerosis and endothelial dysfunction, but their effects for children late after KD complicated with coronary arterial abnormality (CAA) has not been evaluated.

**Methods and Results**  The 11 KD children complicated with CAA (mean age 12.9±2.5 years, mean interval from episode 10.77±3.01 years) and 11 age- and gender-matched healthy controls were studied. The KD group received oral simvastatin 10 mg/day for 3 months. Lipid profiles, high-sensitivity C-reactive protein (hs-CRP) and flow-mediated dilation (FMD) of the brachial artery were performed at baseline in both groups and 3 months later in the KD group. At baseline, the KD group had significantly higher hs-CRP level and decreased FMD than the control group. After 3 months’ treatment, the KD group showed a significant reduction in the hs-CRP level and a significant increase in FMD.

**Conclusions**  In this small study, short-term statin therapy appeared to significantly improve chronic vascular inflammation and endothelial dysfunction with no adverse effects in children complicated by CAA late after KD. However, long-term and randomized studies are still needed to make further conclusions.  (*Circ J* 2008; 72: 1583–1587)

**Key Words:** Chronic vascular inflammation; Endothelial dysfunction; Flow-mediated dilation; High-sensitivity C-reactive protein; Kawasaki disease

---

Kawasaki disease (KD), a systemic vasculitis with a predilection for Asian children, has been noted for almost 40 years since its first description in 1967. Concerns have been raised regarding the existence of endothelial damage and the possibility of a predisposition to premature atherosclerosis in young adulthood. Histopathologic and intravascular ultrasound studies have demonstrated extensive fibro-intimal thickening and infiltration of lymphocytes and plasma cells in the coronary arterial walls late after KD, which suggests that chronic low-grade arterial inflammation is possible even years after the acute phase of KD and plays a role in increasing systemic endothelial dysfunction. Furthermore, endothelial dysfunction is also a precursor of atherosclerosis and subsequent coronary artery damage. Statins, hydroxymethylglutaryl coenzyme A reductase inhibitors, have been shown to not only reduce cholesterol levels, but also improve surrogate markers of atherosclerosis and cardiovascular disease. However, the effects of statin therapy for improving chronic vascular inflammation and endothelial dysfunction have not been evaluated in children complicated with coronary arterial abnormality (CAA) late after KD. This study was designed to determine whether statin therapy would improve chronic vascular inflammation and endothelial dysfunction in these children.

**Methods**

**Study Population**

We studied children who were seen during the acute phase of KD and followed up at Kaohsiung Veterans General Hospital: 11 children with KD complicated by a history of documented CAA were recruited as the study group. All children met the previously defined criteria for KD. The exclusion criteria were diagnosis of KD within 12 months of the study, current use of any vasoactive medications, and concomitant conditions such as infectious diseases, chronic inflammatory disease, malignancy, and other serious illness. We selected 11 healthy age- and gender-matched children as the normal control group. These healthy children had been previously discharged from our clinic with the diagnosis of a functional heart murmur and...
In summary, all measurements were performed monthly. Discontinuation criteria included persistent increase of >3-fold the upper limit of normal ALT or AST, or >10-fold increase in the upper limit of normal ALT. The KD group consisted of 11 children (8 males, 3 females) with a mean age of 12.90±2.50 years (range 9.25–16.67 years). Acute KD had occurred at a mean age of 2.13±1.53 years (range 0.67–6.33 years). They had documented CAA and received intravenous immunoglobulin treatment during the acute phase of KD. All had persistent CAA and took low-dose aspirin during the follow-up period (mean protocol. After a 10–15 min rest, the brachial artery in the right antecubital fossa was visualized using an 8–12 MHz linear array transducer (Vivid 7; GE Medical Systems, Horten, Norway). After an optimal longitudinal image of the brachial artery wall was obtained, the baseline vessel diameter was measured. Reactive hyperemia was induced by inflating the blood pressure cuff to 200 mmHg, or at least 50 mmHg above systolic pressure, on the distal forearm for 5 min and then deflating the cuff. End-diastolic images, concurrent with the onset of the QRS complex on ECG, were acquired at baseline and 1 min after cuff deflation. All vessel diameters were calculated as the average of 2 measurements. The percentage change from the baseline diameter to the value during reactive hyperemia was calculated to determine FMD. The intra-observer variability for FMD measurements was 1.6%.

### Measurement of FMD

The assessment of FMD was performed as described previously. In summary, all measurements were performed in the morning after an overnight fast. All children were advised against consuming alcohol and caffeine-containing beverages, and against performing heavy exercise on the day before the examination. All subjects were studied while supine in a temperature-controlled room (25°C). All measurements were performed by the same operator who was unaware of the medical history of the subjects and the study protocol. After a 10–15 min rest, the brachial artery in the right antecubital fossa was visualized using an 8–12 MHz linear array transducer (Vivid 7; GE Medical Systems, Horten, Norway). After an optimal longitudinal image of the brachial artery wall was obtained, the baseline vessel diameter was measured. Reactive hyperemia was induced by inflating the blood pressure cuff to 200 mmHg, or at least 50 mmHg above systolic pressure, on the distal forearm for 5 min and then deflating the cuff. End-diastolic images, concurrent with the onset of the QRS complex on ECG, were acquired at baseline and 1 min after cuff deflation. All vessel diameters were calculated as the average of 2 measurements. The percentage change from the baseline diameter to the value during reactive hyperemia was calculated to determine FMD. The intra-observer variability for FMD measurements was 1.6%.

### Statistical Analysis

Analyses were performed using SPSS 10.0 for Windows software (Chicago, IL, USA). All values are expressed as mean±SD unless otherwise specified. For comparison of baseline characteristics of the normal control vs the KD study group, either Student’s t-test for parametric continuous variables or Wilcoxon’s rank-sum test for non-parametric continuous variables was performed. Mean values before and after statin therapy in the KD group were compared by using a paired sample t-test or Wilcoxon’s signed-rank test. A p value <0.05 was considered statistically significant.

### Results

#### Characteristics of the Study Subjects

The KD group consisted of 11 children (8 males, 3 females) with a mean age of 12.90±2.50 years (range 9.25–16.67 years). Acute KD had occurred at a mean age of 2.13±1.53 years (range 0.67–6.33 years). They had documented CAA and received intravenous immunoglobulin treatment during the acute phase of KD. All had persistent CAA and took low-dose aspirin during the follow-up period (mean

---

**Table 1 Baseline Characteristics of KD Children and Normal Controls**

<table>
<thead>
<tr>
<th></th>
<th>KD with CAA</th>
<th>Normal controls</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>11</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>12.90±2.50</td>
<td>12.97±2.42</td>
<td>0.950</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>8/3</td>
<td>8/3</td>
<td>1.000</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.18±9.10</td>
<td>20.02±6.00</td>
<td>0.347</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>107±16</td>
<td>114±15</td>
<td>0.250</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>57±7</td>
<td>56±6</td>
<td>0.793</td>
</tr>
</tbody>
</table>

*Data are means±SD. KD, Kawasaki disease; CAA, coronary arterial abnormality; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.*

**Table 2 Serum Lipid Profiles in Normal Controls and KD Children After 3 Months of Statin Therapy**

<table>
<thead>
<tr>
<th></th>
<th>Normal controls</th>
<th>KD with CAA</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mg/dL)</td>
<td>162±21</td>
<td>170±31</td>
<td>0.015</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>91±11</td>
<td>97±17</td>
<td>0.854</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>53±9</td>
<td>51±11</td>
<td>0.05</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>122±41</td>
<td>118±46</td>
<td>0.755</td>
</tr>
</tbody>
</table>

*Data are means±SD; *p<0.001. TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; TG, triglycerides. Other abbreviations see in Table 1.*
follow-up interval 10.77±3.01 years; range 6.25–15.75 years). Clinical characteristics showed no significant differences with regard to gender, age, BMI, and blood pressure between the KD study group and normal control group. Their clinical characteristics are summarized in Table 1.

Serum Lipid Profiles, hs-CRP and FMD at Baseline in Both Groups

Serum lipid profiles at baseline in both groups are shown in Table 2. At baseline, TC, LDL-C, HDL-C and TG levels were not significantly different. The hs-CRP and FMD at baseline in both groups are shown in Fig 1; hs-CRP was significantly higher in the KD group compared with the normal group (0.430±0.225 mg/L vs 0.045±0.028 mg/L, p<0.001). With regard to endothelial function, FMD was significantly reduced in the KD group compared with the normal group (6.12±1.61% vs 13.11±1.00%, p<0.001).

Change in Lipid Profiles in the KD Group After 3 Months of Treatment

The TC level decreased 8.6% from 170±31 mg/dl at baseline to 154±20 mg/dl after 3 months of treatment (p=0.015). The LDL-C level decreased 12.4% from 97±17 mg/dl at baseline to 85±14 mg/dl (p<0.001), and the HDL-C level increased 6.8% from 51±11 mg/dl at baseline to 55±13 mg/dl (p=0.050). The TG level did not change significantly from 118±46 mg/dl at baseline to 117±34 mg/dl (p=0.755). The changes in the serum lipid profiles of the KD group are illustrated in Table 2.

Changes in hs-CRP and FMD in the KD Group After 3 Months of Treatment

Serum hs-CRP level decreased 51.6% significantly from 0.430±0.225 mg/L at baseline to 0.209±0.098 mg/L after 3 months of treatment (p=0.001). This post-treatment level was still significantly higher than that of the normal group (0.209±0.098 mg/L vs 0.045±0.028 mg/L, p<0.001) (Fig 1A). FMD increased 76.9% from 6.12±1.61% at baseline to 10.32±1.58% (p=0.001). The post-treatment FMD in the KD group improved, but was still significantly lower than that in the normal group (10.32±1.58% vs 13.11±1.00%, p<0.001) (Fig 1B). There were no significant differences in the safety measurements (ALT, AST, and CK levels) at baseline and after 3 months therapy. No adverse events concerning statins were reported during the study.

Discussion

Our study results reveal that ongoing chronic vascular inflammation and endothelial dysfunction exist in children complicated with CAA late after KD, reflected in the increased hs-CRP level and reduced FMD. Our results also show that statin therapy significantly improved chronic vascular inflammation and endothelial dysfunction in these patients after short-term treatment, without adverse effects on liver or muscle tissue. To the best of our knowledge, this is the first study to assess the effects of statin therapy on lipoprotein profiles, vascular inflammation and endothelial dysfunction in children late after KD.

Lipid abnormalities in the acute phase of KD, with decreased TC and HDL-C levels, have been well documented in other studies. Whether such alterations of the lipid profile persist late after KD remains controversial. Recently, Niboshi et al used adult KD data to show there was no difference in terms of the lipid profile between 35 KD adult (mean interval time, 24.1 years, age 20–35 years) and 36 healthy adults. In the present study, we also did not find any significant difference in the lipid profiles of the KD group (mean interval time, 10.77 years) and those of the normal controls. However, we believe that all these studies, including ours, are cross-sectional without a large number of subjects, so the findings will not represent the long-term longitudinal lipid profile changes in KD. In addition, our study also demonstrated that 3 months of statin treatment in KD children complicated with CAA could significantly reduce TC and LDL-C levels and increase the HDL-C level. Our results suggest a positive effect of statin therapy on the lipid profile in the chronic stage of KD.

CRP is well-established as a powerful marker of chronic vascular inflammation, but was recently found to also reflect numerous effects on endothelial cells, which could support its role in atherosclerosis. These effects include inhibition of nitric oxide (NO) production, upregulation of interleukin-6, and increased expression of adhesion molecules, etc. Therefore, CRP may itself be associated with chronic endothelial dysfunction, and thus present a potential target for
the treatment of atherosclerosis in KD patients. Consistent with previous studies, in this study the hs-CRP value was still significantly higher in KD children complicated with CAA compared with the normal controls. These findings demonstrate that chronic low grade inflammation can persist late after acute KD. In addition, our study also demonstrated a significant reduction in the serum hs-CRP level after short-term statin treatment, although it was still higher than in the normal controls. We believe that statins are effective in reducing the hs-CRP level.

Endothelium-dependent FMD of the brachial artery has been used to assess endothelial function, mainly the NO-releasing function of the endothelium. Several previous reports have shown that there is systemic endothelial dysfunction late after the onset of KD, as reflected in the FMD of the brachial artery, particularly in children with CAA. However, other reports found that systemic endothelial dysfunction was not present late after KD and did not find any relationship with coronary artery involvement. In our small study, we found significantly decreased FMD of the brachial artery in the KD patient complicated with CAA. These discrepancies may be related to different racial and KD characteristics of the patient and normal control subject populations, acute-stage therapeutic regimens, length of follow-up, relatively small studies or ultrasonographic assessment faults. These all need long-term international studies to assess the impact of KD on vascular health. However, we also demonstrated an improvement of endothelial function in KD patients after short-term statin therapy, and this may establish an effective treatment strategy for atherosclerosis late after KD.

We showed that short-term administration of statins improved chronic vascular inflammation and endothelial dysfunction in KD patients complicated with CAA. Some previous findings may explain these beneficial effects of statins. Statins not only reduce the LDL-C level, but also have several important pleiotropic properties, such as improvement of endothelial dysfunction, inhibition of inflammatory responses, stabilization of atherosclerotic plaques, and modulation of procoagulant activity and platelet function. A possible mechanism for this action of statins is that inhibition of cholesterol synthesis interferes with the formation of lipid rafts on the surface of lymphocytes, which in turn interferes with lymphocyte function and thereby reduces inflammation. Recent studies also show that the cholesterol-independent effect of statins may be a direct improvement of endothelial function by increasing its NO production, promoting re-endothelialization after arterial injury and inhibiting inflammatory responses within the vessel wall. We speculate that statins improve chronic vascular inflammation and endothelial dysfunction in late KD patients through these same mechanisms.

A previous study demonstrated that peripheral endothelial dysfunction in hypercholesterolemic patients can be completely reversed after short-term statin therapy. However, in patients with chronic coronary artery disease, statin therapy can only attenuate the acetylcholine-induced "paradoxical" vasoconstriction, but has no effect on endothelium-dependent vasodilation. Those findings suggest that statin therapy to improve endothelial dysfunction should be initiated at an early reversible stage, before the onset of severe macrovascular structural abnormalities. Recent studies demonstrate that subclinical atherosclerosis develops early in KD patients which makes early initiation of statin therapy in KD patients an important issue. For late-stage KD patients complicated with CAA, we believe that early statin therapy may be helpful in restoring endothelial dysfunction in the reversible stage and prevent future cardiovascular events.

In children with familial hypercholesterolemia, previous studies showed that statins significantly improved lipid abnormalities and endothelial function without serious side-effects. Until now, only 4 statins, including simvastatin, have been approved by the US Food and Drug Agency for use in children. We chose simvastatin for the study regimen because low-dose short-term simvastatin has been proven to significantly improve lipoprotein profile and endothelial dysfunction in such children. We did not try to ascertain which statin or dosage is effective in KD children. Besides, we still did not answer the question of the age at which statin treatment should be initiated in terms of safety and cardiovascular disease risk reduction, and whether delaying therapy until adulthood may be just as beneficial as treatment in childhood. Additional research with more rigorous study designs is needed in the future.

Study Limitations
This was not a placebo-controlled study, nor were lifestyle changes actively monitored or controlled. The relatively small number of children enrolled and the short-term intervention could have introduced certain bias in the results. We did not clarify the effects of the treatment on endothelial function during the acute and chronic stages of KD. Besides, this was a cross-sectional and short-term clinical trial, and the beneficial effect of statin therapy in KD children remains to be determined. Although no toxicity, serious adverse or side-effects were reported by the children during the course of our study, the duration of the present study is too short to draw conclusions regarding the safety of long-term use of statins in KD children. A long-term study including a large sample is required to elucidate these factors.

In our ongoing studies, we have designed a randomized, placebo-controlled, crossover design to evaluate the effect of statins and their withdrawal on chronic vascular inflammation and endothelial dysfunction. We found a rebound effect on endothelial function after discontinuation of statin treatment, and no side-effects have been recorded to date (unpublished data).

Conclusions
Chronic vascular inflammation and endothelial dysfunction persist in KD patients with CAA, even late after the acute stage. Although this was a limited study with a small sample, our data show short-term statin therapy may significantly improve chronic vascular inflammation and endothelial dysfunction with no adverse effects in children complicated by CAA late after KD.

Acknowledgments
This study was supported by a grant (VGHKS-96-052) from Kaohsiung Veterans General Hospital and Kaohsiung Municipal United Hospital, Taiwan.

References


