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Evaluation by High-Resolution Ultrasonography of Endothelial Function in Brachial Artery After Kawasaki Disease and the Effects of Intravenous Administration of Vitamin C

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Previous studies in patients with a history of Kawasaki disease (KD) have focused on the endothelial function of the coronary arteries and that of the systemic arteries is not fully understood. Furthermore, the effect of vitamin C on systemic vascular endothelial function after KD has not yet been elucidated. In the present study, 39 patients (age, 7.1±2.7 years) at 1–10 years after acute KD were compared with 17 matched healthy subjects (7.0±3.1 years). High-resolution ultrasonography was used to analyze brachial artery responses to reactive hyperemia (with increased flow causing endothelium-dependent dilation) and sublingual nitroglycerin (causing endothelium-independent dilation) after KD, and to investigate whether the acute administration of vitamin C can restore systemic endothelial dysfunction. The percent change in diameter of the brachial artery induced by reactive hyperemia in the patients with a history of KD (6.2±3.9%) was significantly less than that in the control group (14.1±6.8%, p<0.0001). No significant difference could be found in the percent change in diameter induced by sublingual nitroglycerin between the controls (33.2±13.7%) and the patients (30.6±9.2%, p=0.49). There was no significant difference in percent change in diameter of the brachial artery induced by reactive hyperemia between the patients who received gamma globulin (6.0±4.0) and those who did not (7.9±3.3, p=0.33). Intravenous infusion of vitamin C significantly increased the percent change in diameter of the brachial artery induced by reactive hyperemia in 19 patients with history of KD (6.6±3.5% to 13.0±5.5%, p<0.0001). After placebo administration in 20 patients with history of KD there was no significant increase in the percent change in the diameter of the brachial artery induced by reactive hyperemia (6.5±4.5% to 7.3±4.9%, p=0.20). The decreased percent change in the diameter of the brachial artery induced by reactive hyperemia in patients with a history of KD compared with the healthy children indicates that systemic endothelial dysfunction exists after KD. Although it is not influenced by early treatment with high-dose gamma globulin in the acute stage of KD, systemic vascular endothelial function can be restored by acute intravenous administration of vitamin C. (*Circ J* 2002; **66:** 908–912)

Key Words: Endothelial function; Gamma globulin; Kawasaki disease; Vitamin C

Kawasaki disease (KD) is an acute febrile disease with a systemic vasculitis that predominantly occurs in infancy and early childhood[1] In the acute stage, a coronary aneurysm may form and has been associated with myocardial infarction and death[2] Both histopathological[3] and intravascular ultrasound[4,5] studies have demonstrated marked thickening of the intimal layers of the coronary arteries after KD and there is now evidence that flow-mediated endothelium-dependent vasodilation is abnormal after KD[6–8] However, those studies in patients with a history of KD have focused on vascular endothelial function in the coronary arteries only[6,7] and the systemic arterial endothelial function is not fully understood[8] Furthermore, the previous studies have been mainly confined to patients who had not received high-dose gamma globulin treatment[6–8] and there are no data on the influence of gamma globulin therapy during the acute stage of KD on later abnormalities of endothelial function.

In experimental models it has been found that flow-mediated dilation depends on the ability of the endothelium to release nitric oxide in response to shear stress[9] This dilation can be blocked by intra-arterial infusion of N-monomethyl-L-arginine, a specific antagonist of nitric oxide production, indicating that flow-mediated vasodilation in large arteries reflects endothelial nitric oxide activity[10,11] Vitamin C is a water-soluble antioxidant and its administration has been shown to improve endothelial dysfunction in patients with diabetes[12] and congestive heart failure[13] by increasing the nitric oxide activity. However, its effect on systemic endothelial function after KD is not known. Therefore, we used high-resolution ultrasonography to (1) analyze endothelium-dependent vasodilation in the brachial artery after KD, (2) determine whether the use of gamma globulin therapy in the acute stage of KD affects the later endothelial dysfunction, and (3) investigate whether the acute administration of vitamin C can restore

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such systemic endothelial dysfunction.

Methods

Study Population

The patients who had had acute KD more than 1 year previously were enrolled. KD was diagnosed by standard criteria.[14] Subjects with evidence of smoking, diabetes mellitus, hypertension and hypercholesterolemia were excluded from the study population. As a result, 39 patients (28 male) with a mean age of 7.1±2.7 years (range, 3.0–14.7 years) were studied 1–10 years (3.4±2.1 years) after acute KD, which had occurred at 0.3–10 years of age (3.7±2.8 years). During the acute stage, 6 patients had dilation of the proximal left anterior descending and/or right coronary arteries with a diameter greater than 3.5 mm. The dilated coronary arteries regressed during follow-up in 3 patients and the other 3 still had dilated coronary arteries greater than 3.5 mm at the time of the present study. Intravenous gamma globulin (2 g/kg as a single infusion over 12 h) was given to 34 patients within 10 days of the onset of fever. All patients received aspirin with an initial high dose of 80–100 mg/kg per day orally in 4 equally divided doses until they were afebrile for 3 days, followed by a low dose of 3–5 mg/kg per day orally for 6–8 weeks. The control group consisted of 17 healthy age- and sex- matched subjects (mean age: 7.0±3.1 years, range: 3.6–12 years) without the risk factors for endothelial damage listed earlier. The study was approved by the local ethics committee, and informed consent was obtained from the parents of all subjects.

Measurement of Flow-Mediated and Nitroglycerin-Induced Dilations of the Brachial Artery

Arterial endothelium-dependent and -independent vasodilation were studied noninvasively in a quiet and temperature-controlled (20–23°C) room. Brachial artery responses to endothelium-dependent and -independent stimuli were assessed according to the method described by Celermajer et al.[15] All examinations were performed by the same examiner throughout the study. Using a 4–10 MHz high-resolution linear array transducer (Vivid 7, GE Medical System, Milwaukee, WI, USA and Sonos 5500, Hewlett-Packard Co, Andover, MA, USA), the diameter of the right brachial artery was measured from 2-dimensional (D) images (1) at rest, during reactive hyperemia, which induces endothelium-dependent vasodilation, and again at rest, and (2) after sublingual nitroglycerin (NTG) administration, which causes endothelium-independent vasodilation. If the children were uncooperative, they were given 10 ml 10% chloral hydrate (Gutian Pharmaceuticals, Fujian, China) to induce sleep. The subjects lay on the examination bed for at least 10 min before the initial ultrasound examination of the brachial artery and remained supine throughout the study.

The right brachial artery was scanned longitudinally 3–5 cm above the elbow, with great care taken to maximize vessel diameter and to provide optimal blood-vessel wall definition. Depth and gain settings were optimized to identify the lumen-to-vessel wall interface. The blood flow velocity spectrum of the right brachial artery was recorded by pulsed-wave Doppler method, with the sample volume positioned on the center of the artery. Blood flow velocity was corrected for the incident angle of the Doppler beam to the blood flow. Machine operating variables were not changed throughout each study.

When a satisfactory transducer position was found, the skin was marked for reference for later examinations and the arm was kept in the same position throughout the study. Baseline 2-D images and the blood flow velocity spectrum of the right brachial artery were then recorded. The blood pressure cuff placed around the forearm was inflated and pressure was kept at 200 mmHg for 5 min. Increased flow was then induced by sudden cuff deflation. The second recording of the 2-D images and blood flow velocity spectrum was performed 30 s before release of the cuff and continued for a further 90 s after cuff deflation. After 15 min, further resting recordings of 2-D images and the blood flow velocity spectrum were taken to confirm vessel recovery. Sublingual administration of 0.3 mg NTG followed, and 3–5 min later 2-D images and the blood flow velocity spectrum were recorded. All recordings were stored on a magnetic optical disk for later analysis.

Arterial diameter and blood flow measurements were performed from the magnetic optical disk recording by a single observer blinded to the clinical details and the stage of the experiment. The diameter of the brachial artery was measured from the near to the far interface between the media and the adventitia from the 2-D images. The mean diameter was calculated from 5 consecutive cardiac cycles. All measurements were made at end-diastole to avoid possible errors resulting from variable arterial compliance. Brachial artery diameter measurements after reactive hyperemia were taken 60 s after cuff deflation. The percent change in diameter caused by reactive hyperemia was calculated by dividing the difference from baseline diameter by the baseline value. The percent change in diameter caused by NTG administration was also calculated in the same way. Measurements of the velocity time integral after reactive hyperemia were taken 10 s after cuff deflation. The envelope of the Doppler blood flow velocity spectrum was traced to calculate the velocity time integral. Blood flow volume was calculated by multiplying the vessel cross-sectional area by the velocity time integral of the Doppler blood flow velocity spectrum and the heart rate. Percent changes in blood flow volume during reactive hyperemia were calculated by dividing the difference from the baseline flow volumes by the baseline values. This technique has been shown to be reproducible and reliable, and a previous study showed that the mean and standard deviation of differences between observations were 0.06±0.02 mm (intraobserver) and 0.1±0.03 mm (interobserver).[16]

Protocol

The endothelium-dependent and -independent vasodilation of the brachial artery was evaluated in 39 patients with a history of KD and in 17 control subjects to elucidate whether or not brachial artery endothelial dysfunction exists after KD. Subsequently, the patients received an intravenous infusion of 100 ml of either 0.9% saline containing 3 g of vitamin C (Gutian Pharmaceuticals) over 10 min or placebo (100 ml 0.9% saline without vitamin C). Both the vitamin C and placebo infusions were randomly allocated: 19 patients received vitamin C and 20 patients received the placebo. The brachial vasodilation was reassessed before and after the infusions.

Statistical Analysis

All values are expressed as mean ± 1 SD. Group comparisons were carried out by unpaired t-test. Paired Student's t

Table 1 Characteristics of the Study Population

	Control subjects (n=17)	KD patients (n=39)	p value
Age (years)	7.0±3.1	7.1±2.7	0.4
F/M	4/13	11/28	0.8
Total C (mmol/L)	3.89±0.99	4.06±1.08	0.6
HDL-C (mmol/L)	1.48±0.54	1.54±0.44	0.7
LDL-C (mmol/L)	2.15±1.08	2.18±0.99	0.5
Triglyceride (mmol/L)	0.58±0.29	0.64±0.32	0.7

Data are mean±standard deviation or number of subjects.
KD, Kawasaki disease; C, cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Table 3 Brachial Artery Responses in KD Patients With and Without Early Treatment With High Dose Gamma Globulin

	With gamma globulin (n=34)	Without gamma globulin (n=5)	p value
B-Dia (mm)	2.2±0.3	2.4±0.4	0.29
RH-Dia (mm)	2.4±0.3	2.6±0.5	0.17
B-BFV (ml/min)	32.3±18.4	35.3±20.3	0.74
%Dia-RH (%)	6.0±4.0	7.9±3.3	0.33
%Dia-NTG (%)	30.7±9.0	30.0±11.4	0.86
%BFV-RH (%)	336.6±134.1	381.3±120.0	0.49

Data are mean±standard deviation.
Abbreviations as in Table 2.

test was utilized for comparisons of the data in the subjects taking vitamin C and the placebo. A p value less than 0.05 was taken to define statistical significance.

Results

Patient Characteristics (Table 1)

The patients with a history of KD and the controls were well matched for age and gender. There were no significant differences in serum concentrations of total cholesterol, triglyceride, and high- and low-density lipoprotein cholesterol between the 2 groups.

Flow-Mediated and NTG-Induced Dilations of the Brachial Artery (Table 2)

There were no significant differences in baseline artery diameter, baseline blood flow volume, and the percent change in blood flow volume during reactive hyperemia between controls and patients. During reactive hyperemia, the diameter of the brachial artery increased significantly both in the control group (from 2.2±0.2 to 2.5±0.4 mm, p<0.0001) and the patients (from 2.3±0.3 to 2.4±0.3 mm, p<0.0001), but the percent change was significantly lower in the patients with a history of KD (6.2±3.9%) than in the control group (14.1±6.8%, p<0.0001). No significant difference could be found in the percent change in diameter induced by sublingual NTG between the controls (33.2±13.7%) and the patients (30.6±9.2%, p=0.49).

Influence of Early Treatment With High-Dose Gamma Globulin and Early Coronary Artery Abnormalities on Dilation of the Brachial Artery

Flow-mediated and NTG-induced dilation of the brachial artery in patients who received high-dose gamma globulin and those who did not during the acute stage of KD are shown in Table 3. No significant difference could be found in the percent change in diameter of the brachial artery induced by reactive hyperemia between the patients who received gamma globulin (6.0±4.0) and those who did not (7.9±3.3, p=0.33). The percent change in the diameter of the brachial artery induced by reactive hyperemia did not differ in the patients who had a detectable coronary dilation in the acute stage (Table 4).

Table 2 Brachial Artery Responses in KD Patients and Control Subjects

	Control subjects (n=17)	KD patients (n=39)	p value
B-Dia (mm)	2.2±0.2	2.3±0.3	0.56
RH-Dia (mm)	2.5±0.4	2.4±0.3	0.46
B-BFV (ml/min)	32±13	33±18	0.84
%Dia-RH (%)	14.1±6.8	6.2±3.9	<0.0001
%Dia-NTG (%)	33.2±13.7	30.6±9.2	0.49
%BFV-RH (%)	296.8±189.8	342.5±131.7	0.35

Data are mean±standard deviation.
KD, Kawasaki disease; B-Dia, baseline diameter; RH-Dia, diameter during reactive hyperemia; B-BFV, baseline blood flow volume; %Dia-RH, percent change in diameter induced by reactive hyperemia; %Dia-NTG, percent change in diameter induced by nitroglycerin; %BFV-RH, percent change in blood flow volume induced by reactive hyperemia.

Table 4 Brachial Artery Responses in KD Patients With and Without Early Coronary Artery Dilation

	Without CA dilation (n=33)	With CA dilation (n=6)	p value
B-Dia (mm)	2.3±0.3	2.2±0.2	0.79
RH-Dia (mm)	2.4±0.4	2.3±0.2	0.74
B-BFV (ml/min)	34.0±19.3	25.3±11.0	0.29
%Dia-RH (%)	6.3±4.3	5.7±1.4	0.71
%Dia-NTG (%)	30.2±9.7	33.3±5.0	0.54
%BFV-RH (%)	325.7±130.6	431.8±106.1	0.07

Data are mean±standard deviation.
CA, coronary artery; other abbreviations as in Table 2.

Effect of Vitamin C Administration on the Flow-Mediated Dilation of the Brachial Artery (Table 5)

Intravenous infusion of vitamin C significantly increased the percent change in diameter of the brachial artery induced by reactive hyperemia in 19 patients with a history of KD (6.6±3.5% to 13.0±5.5%, p<0.0001). No significant increase was seen in the percent change in diameter of the brachial artery induced by reactive hyperemia in 20 patients after placebo administration (6.5±4.5% to 7.3±4.9%, p=0.20). There was no significant change in the percent change in the diameter of the brachial artery after sublingual administration of NTG in both the19 patients receiving vitamin C (26.5±6.3% to 26.1±6.0%, p=0.80) and the 20 patients receiving placebo (33.5±10.3% to 30.1±9.6%, p=0.08).

Discussion

The present study demonstrated that systemic endothelial dysfunction exists after KD and although it is not affected by early treatment with high-dose gamma globulin in the acute stage of KD, it can be restored by acute intravenous administration of vitamin C.

It has long been known that coronary artery aneurysms occur in a minority of children with acute KD[17] and much attention has been focused on the long-term outcome of this subgroup![18] Previous intravascular ultrasound studies

Table 5 Effects of Vitamin C on Brachial Artery Response in KD Patients

	Vitamin C (n=19)			*Placebo (n=20)*		
	Before	*After*	*p value*	*Before*	*After*	*p value*
B-Dia (mm)	*2.3±0.3*	*2.3±0.3*	*0.38*	*2.3±0.3*	*2.4±0.4*	*0.08*
RH-Dia (mm)	*2.4±0.4*	*2.6±0.3*	*0.0002*	*2.4±0.3*	*2.5±0.4*	*0.08*
B-BFV (ml/min)	*33±24*	*28±16*	*0.46*	*34±15*	*42±26*	*0.13*
%Dia-RH (%)	*6.6±3.5*	*13.0±5.5*	*<0.0001*	*6.5±4.5*	*7.3±4.9*	*0.20*
%Dia-NTG (%)	*26.5±6.3*	*26.1±6.0*	*0.80*	*33.5±10.3*	*30.1±9.6*	*0.08*
%BFV-RH (%)	*342±162*	*519±249*	*0.07*	*361±117*	*475±201*	*0.15*

Data are mean±standard deviation.
Abbreviations as in Table 2.

performed after KD showed an increase in intimal thickness during the acute phase of KD, even in angiographically normal coronary segments that did not have aneurysmal lesions.[4,5] Using quantitative angiography combined with intracoronary acetylcholine infusion, Mitani et al demonstrated that in patients who had recovered from KD the endothelium-dependent vasodilation of coronary arteries was impaired despite an angiographically normal appearance.[7] However, KD is characterized by a systemic vasculitis; histopathological findings in acute KD are widespread vascular inflammation with endothelial edema and necrosis and leukocyte infiltration involving coronary and other medium-sized muscular arteries, even in children without echocardiographically detectable aneurysms.[1,9] Therefore, endothelial dysfunction can develop in not only the coronary arteries, but also in the systemic vessels. Dhillon et al showed that in patients with history of KD there is impaired flow-mediated vasodilation in the brachial artery compared with that in normal children, suggesting that endothelial dysfunction is present even in arteries remote from the coronary circulation.[8] However, there have been conflicting results regarding the systemic effects of KD,[7] although endothelial dysfunction in the coronary artery has been confirmed.[6] Mitani et al[7] could not find a significant difference in the percent change in the diameter of the femoral artery induced by reactive hyperemia between patients with a history of KD and normal subjects, indicating that the systemic endothelial function was preserved in patients with history of KD. However, their study was limited by the relatively short time (45 s) allowed to measure vessel diameter after cuff release. A previous study has demonstrated a progressive increase in percent diameter change following cuff release after 5 min of occlusion and that this increase in percent diameter change peaked at 1 min.[20]

Endothelial dysfunction in large arteries is an important early event in the atherogenic process and abnormal endothelial function was recently, demonstrated in patients with coronary spastic angina.[21] Using the same method as Dhillon et al,[8] we demonstrated that there is endothelial dysfunction in the brachial artery after KD. Furthermore, we also showed that there was no significant difference in the percent change in diameter of the brachial artery induced by reactive hyperemia between the patients who received gamma globulin and those who did not, indicating that late abnormalities of brachial endothelial function are not influenced by early gamma globulin therapy.

This study also demonstrated that acute intravenous administration of vitamin C improved the flow-mediated vasodilation of the brachial artery in patients with history of KD. Vitamin C had no effect on the baseline vessel diameter or on NTG-induced endothelium-independent vasodilation. Our findings suggest that vitamin C restores brachial artery endothelial dysfunction and although the precise mechanisms of endothelial dysfunction and the beneficial effect of vitamin C in patients with history of KD remain undetermined, we propose some possible explanations. Ogawa et al demonstrated a high level of soluble endothelin-1 not only in the acute phase of KD but also in the recovery stage,[22] and it has also been demonstrated that the plasma concentration of endothelin-1 significantly increased after dobutamine stress after KD.[23] A recent study showed that endothelin-1 could induce an increase in superoxide anion production,[24] which rapidly reacts with and breaks down nitric oxide. Vitamin C is a potent water-soluble antioxidant and effective scavenger of free radicals, such as the superoxide anion.[25] Acute intravenous administration of vitamin C has improved the flow-mediated vasodilation in the brachial artery in patients with congestive heart failure through the increased availability of nitric oxide,[13] and it is possible that the improvement in patients with history of KD is via the same mechanisms.

Study Limitations

Systemic endothelial function was tested 3.4±2.1 years after acute KD, which is a relatively short follow-up period. Although the present study showed brachial endothelial dysfunction, further investigation with a long follow-up period is needed to clarify the chronic effects of KD on the systemic endothelial function.

Another limitation of the study is the relatively small number of subjects and further study in large numbers of patients with KD is needed to confirm the systemic endothelial function after KD.

Conclusion

Our study showed a decrease in the percent change in the diameter of the brachial artery induced by reactive hyperemia in patients with a history of KD compared with the healthy children, indicating that systemic endothelial dysfunction exists after KD. Although it is not influenced by early treatment with high-dose gamma globulin in the acute stage of KD, the systemic endothelial dysfunction after KD can be restored by acute intravenous administration of vitamin C.

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