Xuezhikang, an Extract of Cholestin, Protects Endothelial Function Through Antiinflammatory and Lipid-Lowering Mechanisms in Patients With Coronary Heart Disease

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Background—Endothelial dysfunction is associated with inflammation and postprandial hypertriglyceridemia. Xuezhikang, an extract of Cholestin, a dietary supplement, has lipid-modulating and antiinflammatory effects. We explored the effects of xuezhikang on endothelial function and high-sensitivity C-reactive protein (hs-CRP) in patients with coronary heart disease (CHD).

Methods and Results—We prospectively randomized 50 CHD patients to xuezhikang 1200 mg/d or placebo for 6 weeks. Fasting hs-CRP concentrations, flow-mediated vasodilation (FMD) at 0 and 4 hours, and lipid parameters at 0, 2, 4, and 6 hours were monitored after a high-fat meal (800 calories; 50 g fat) in all patients. All patients underwent a high-fat meal test at the beginning of the study and after 6 weeks of treatment. Postprandial FMD was significantly worse at 4 hours after a high-fat meal ($P<0.05$), and this was associated with the area under the triglyceride curve (TG-AUC) ($r=0.345$, $P<0.01$). After 6 weeks of xuezhikang, fasting hs-CRP levels and TG-AUC ($P<0.001$ for each) decreased. Furthermore, preprandial and postprandial FMD significantly improved ($P<0.001$). There were no significant changes in serum lipids and FMD in the placebo arm. In multivariable regression analysis, changes in TG-AUC and fasting hs-CRP levels were predictive of improvement in preprandial FMD ($P<0.05$).

Conclusions—Xuezhikang effectively improved preprandial and postprandial endothelial function through its potent antiinflammatory and lipid-lowering effects. **(*Circulation*. 2004;110:915-920.)**

Key Words: postprandial period ■ vasodilation ■ blood flow ■ coronary disease ■ xuezhikang

Endothelial dysfunction occurs early in atherosclerosis and is considered to play a significant role in atherothrombosis. Acute endothelial dysfunction after postprandial hypertriglyceridemia exists not only in patients with coronary heart disease (CHD) but also in healthy subjects.[1,2] Moreover, postprandial triglyceride-rich lipoproteins and remnants directly impair endothelium-dependent vasodilation in animal models.[3,4] In addition, treatment strategies for lowering postprandial hypertriglyceridemia may lead to a reduction in CHD risk.[5]

Inflammation is closely associated with endothelial dysfunction and atherosclerosis. Recent observational data indicate that treating inflammation may lead to a decrease in cardiovascular mortality.[6,7] Xuezhikang, an extract of Cholestin, has been approved by the Food and Drug Administration as a Chinese red-yeast rice dietary supplement. It contains a family of naturally occurring statins and has a marked modulating effect on lipids and C-reactive protein (CRP) concentrations.[8–12] However, no attention has been directed to the potential effects on endothelial function. The present study was designed to explore the change of flow-mediated vasodilation (FMD) of the brachial artery in response to a high-fat meal before and after 6-week treatment with xuezhikang and its relation to the changes in fasting CRP and postprandial triglyceride concentrations in CHD patients.

Methods

Study Population

The study included 50 consecutive patients with documented CHD who were admitted to our institution between February 2001 and January 2002. CHD was defined as a history of myocardial infarction and/or angiographically proven coronary atherosclerosis in patients with angina pectoris.

Baseline characteristics, including dietary habits, dietary constituents, dietary quantities, and daily activities, were assessed by the Nutrition and Health Questionnaire. The Ethics Committee of Central South University approved the research protocol. All subjects gave fully informed consent before study entry.

Study Design

All subjects underwent a 4-week dietary advisory period before initiation of the study. After 12 hours of overnight fasting, subjects

Received January 22, 2003; de novo received January 13, 2004; accepted April 20, 2004.

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Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/01.CIR.0000139985.81163.CE**

were given a high-fat meal. Blood samples were drawn at 0, 2, 4, and 6 hours. Fasting CRP concentrations and serum total cholesterol, triglyceride, HDL cholesterol (HDL-C), and LDL cholesterol (LDL-C) concentrations during fasting and postprandial states were measured. Endothelial function was evaluated at baseline and 4 hours after the high-fat meal.

Subsequently, patients were randomly divided into 2 groups: 25 patients were treated with xuezhikang (300 mg Cholestin per capsule, WBL Peking University Biotech Co, Ltd) 1200 mg/d, and the rest were given a matching placebo (routine group) for 6 weeks. In addition, all patients were subjected to dietary control and were treated with aspirin (100 mg/d), metoprolol, fosinopril, and nitrates. At the end of the 6 weeks, each subject had the same high-fat meal test again, and the following parameters were measured: fasting CRP, total cholesterol, HDL-C, LDL-C, and triglyceride concentrations during fasting and postprandial states. Endothelial function was also assessed again at baseline and 4 hours postprandially.

Oral High-Fat Tolerance Test

The oral high-fat tolerance test was undertaken as described previously by a nutritionist.[1,13] The high-fat meal consisted of 800 calories with 50 g of fat (345 mg of cholesterol), 28 g of protein, and 60 g of carbohydrates.

Brachial Artery Vasodilation Measurement

Endothelial function was measured by a previously described noninvasive technique.[1,13] All imaging was performed by a single, highly skilled sonographer who was unaware of the study assignment. Brachial artery diameter was imaged with a 10-MHz linear array transducer ultrasound system at a location 3 to 7 cm above the antecubital crease of the right arm. The brachial artery diameters at baseline (D_0) and after reactive hyperemia (D_1) and sublingual nitroglycerine (D_2) were recorded. The FMD $[(D_1-D_0)/D_{0\times}100\%]$ was used as a measure of endothelium-dependent vasodilation. The nitroglycerine-induced vasodilatation (NID) $[(D_2-D_0)/D_{0\times}100\%]$ was used as a measure of endothelium-independent vasodilatation. Arterial blood flow was measured as Doppler flow velocity multiplied by the cross-sectional area (πr^2).

Laboratory Assays

Blood samples were separated at 4°C and stored at −20°C. Serum total cholesterol, triglyceride, HDL-C, and LDL-C concentrations were measured on a Hitachi 7170A analyzer by a specialist who was unaware of the study assignment.

High-sensitivity CRP (hs-CRP) was measured at 550 nm with the use of the Particle Enhanced Immunoturbidimetric Assay (Orion Diagnostica).

TABLE 1. Baseline Characteristics

	Xuzhikang Group (n=25)	Routine Group (n=25)
Age, y	58.2±4.2	59.1±6.3
Gender, male/female	15/10	14/11
Smoker, %	36	40
Body mass index, kg/m^2	25.2±3.4	25.7±2.1
Blood pressure, mm Hg	126/82	127/80
Fasting glucose, mmol/L	5.62±0.48	5.51±0.52
History of hypertension, % (n)	20 (5)	20 (5)
Medication history, % (n)		
β-Blocker	20 (5)	20 (5)
Diuretic	8 (2)	12 (3)
Calcium channel blocker	12 (3)	16 (4)
Nitrate	24 (6)	20 (5)

Statistical Analysis

Data were analyzed with the use of SPSS (version 10.0) and are presented as mean±SD unless otherwise indicated. Log transformation was made for distribution-dependent analyses. Differences between intragroup and intergroup means were analyzed by *t* test or 1-way ANOVA. Coefficients of correlation (*r*) were calculated by the Pearson correlation analysis. Multiple stepwise regression analysis was used to define the influence of the changes of serum lipid and hs-CRP levels on the change of FMD. Postprandial triglyceride area under the curve (TG-AUC) over the fasting concentration was calculated by the trapezoidal method. Statistical significance was assumed at $P<0.05$.

Results

Baseline characteristics of the patients are shown in Table 1. Both groups were similar in regard to age, gender, body mass index, blood pressure, and use of medications such as β-blockers, diuretics, calcium channel blockers, and nitrates. Furthermore, there were no significant differences in fasting lipids, hs-CRP concentrations, and TG-AUC at baseline between the 2 groups (Table 2). Similarly, fasting NID, FMD, and postprandial worsening of FMD were comparable between the xuezhikang group and the placebo group at baseline (Figure 1).

TABLE 2. Baseline and 6-Week Lipid and hs-CRP Levels in the Xuezhikang and Placebo Groups

	Xuzhikang Group (n=25)		Routine Group (n=25)	
	Baseline	6 Weeks	Baseline	6 Weeks
Total cholesterol, mmol/L	5.37±0.51	4.36±0.65*	5.37±0.46	5.30±0.46
HDL-C, mmol/L	1.15±0.20	1.35±0.21*	1.15±0.23	1.15±0.14
LDL-C, mmol/L	3.32±0.38	2.38±0.33*	3.35±0.35	3.26±0.31
Triglyceride, mmol/L	1.77±0.48	1.22±0.36*	1.74±0.35	1.68±0.31
TG-AUC, mmol/L (0.6 h)	6.15±2.78	3.15±1.12*	6.13±2.27	6.02±2.46
hs-CRP, mg/L	2.70 (1.70, 4.13)	1.30 (0.95, 2.05)*	2.70 (1.95, 3.65)	2.10(1.35, 2.85)†
log(hs-CRP)	0.40±0.25	0.11±0.21*	0.39±0.24	0.27±0.21†

Values are mean±SD except that hs-CRP is shown on the original scale (median [lower, upper quartile]) and on the log scale (mean±SD).

*$P<0.001$, †$P<0.05$ compared with baseline.

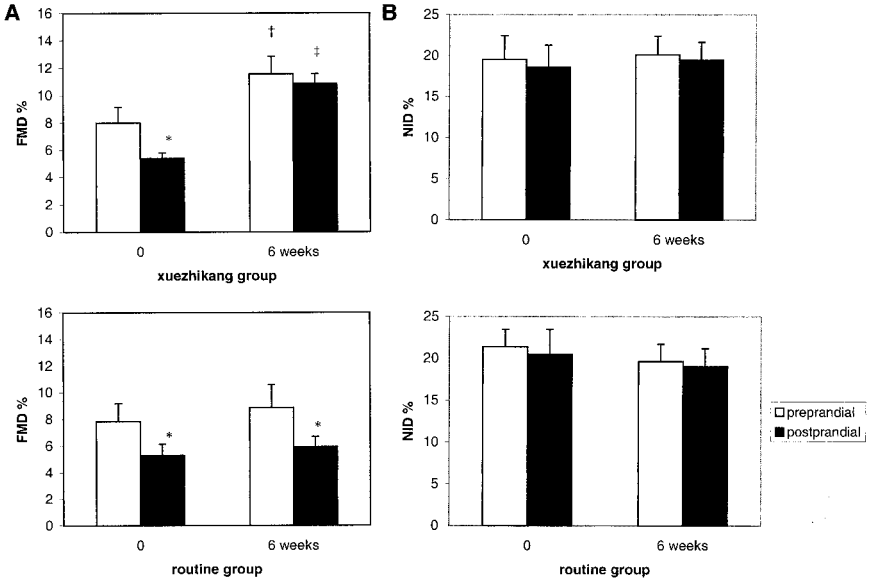

Figure 1. Effects of a high-fat meal on FMD and NID in CHD patients after 6 weeks of xuezhikang treatment vs placebo (routine group). Values are presented as mean±SEM. *$P<0.05$ compared with preprandial FMD within 1 day; †$P<0.05$ compared with preprandial FMD at baseline; ‡$P<0.05$ compared with postprandial FMD at baseline.

The serum total cholesterol, LDL-C, and HDL-C concentrations did not change significantly in the postprandial period (data not shown), whereas the postprandial triglyceride concentrations increased significantly at 2, 4, and 6 hours ($P<0.05$) (Figure 2).

FMD decreased significantly at 4 hours after a high-fat meal (7.91±3.16% versus 5.34±2.78%; $P<0.05$; n=50). Baseline artery diameter, blood flow, reactive hyperemia flow (data not shown), and NID were not affected by the high-fat meal (Figure 1).

After 6 weeks of treatment, the fasting triglyceride, total cholesterol, and LDL-C concentrations decreased, whereas HDL-C concentration increased significantly in response to xuezhikang ($P<0.001$) (Table 2). The postprandial serum triglyceride concentrations at all time points (2, 4, and 6 hours) (Figure 2) and TG-AUC decreased significantly in the xuezhikang group ($P<0.001$), accompanied by a 50% reduction in the fasting hs-CRP concentration (Table 2 and Figure 3). Placebo therapy had no significant effect on the fasting lipids concentrations. Patients treated with xuezhikang had a

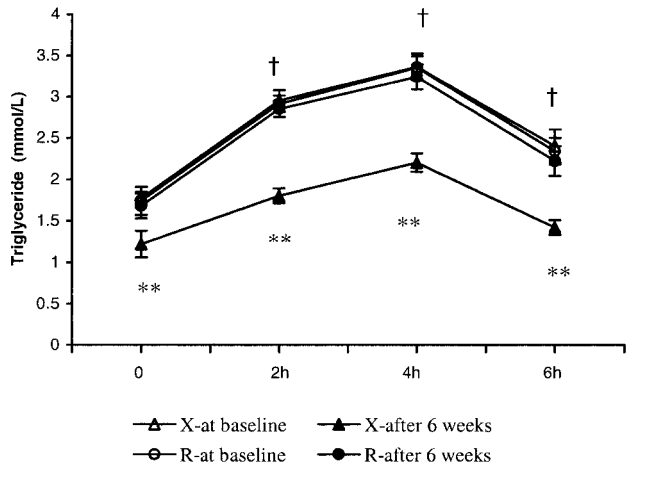

Figure 2. Changes in serum triglyceride concentrations in response to a high-fat meal in the xuezhikang group and placebo (routine) group before and after 6 weeks. Values are presented as mean±SEM. †$P<0.05$ compared with fasting triglyceride concentration; **$P<0.001$ compared with baseline triglyceride concentration at the same time point in the xuezhikang group. X indicates xuezhikang group; R, routine group.

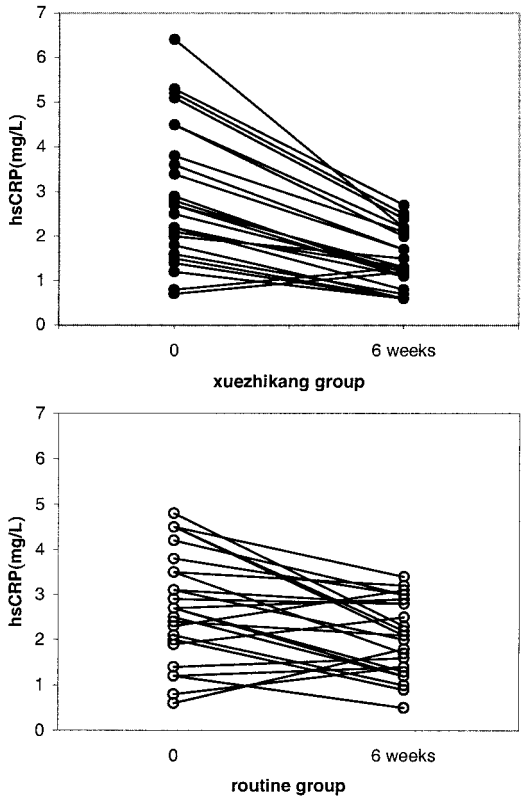

Figure 3. Changes of serum hs-CRP concentrations in CHD patients after 6-week xuezhikang treatment vs placebo (routine group).

significantly greater reduction of hs-CRP concentration than the routine group (50.0% versus 25.4%; $P<0.05$). There was a significant correlation between changes in hs-CRP concentration and TG-AUC in the xuezhikang group ($r=0.441$, $P<0.001$), whereas no significant correlation was seen between the changes in hs-CRP and other lipid parameters (data not shown).

Both preprandial and postprandial FMD significantly improved compared with baseline ($P<0.05$), and no significant worsening of FMD after a high-fat meal was observed in the xuezhikang group. However, individuals in the routine group had no significant change in FMD after 6 weeks, and postprandial impairment was still present in this group. NID did not change during xuezhikang or placebo therapy (Figure 1).

When we analyzed all 50 patients, worsening of postprandial FMD was significantly correlated with TG-AUC ($r=0.345$, $P<0.01$), and improvement of postprandial FMD was correlated with the decrement of TG-AUC ($r=0.455$, $P<0.01$).

The improvement of preprandial FMD was significantly correlated with decrements of TG-AUC ($r=0.427$, $P<0.01$), hs-CRP ($r=0.388$, $P<0.05$), and total cholesterol ($r=0.390$, $P<0.01$) concentrations and the increment of HDL-C concentration ($r=-0.356$, $P<0.05$). In multiple stepwise regression analysis, only the decrements of TG-AUC and hs-CRP concentration independently and significantly predicted the improvement of preprandial FMD ($P<0.05$) (Figure 4).

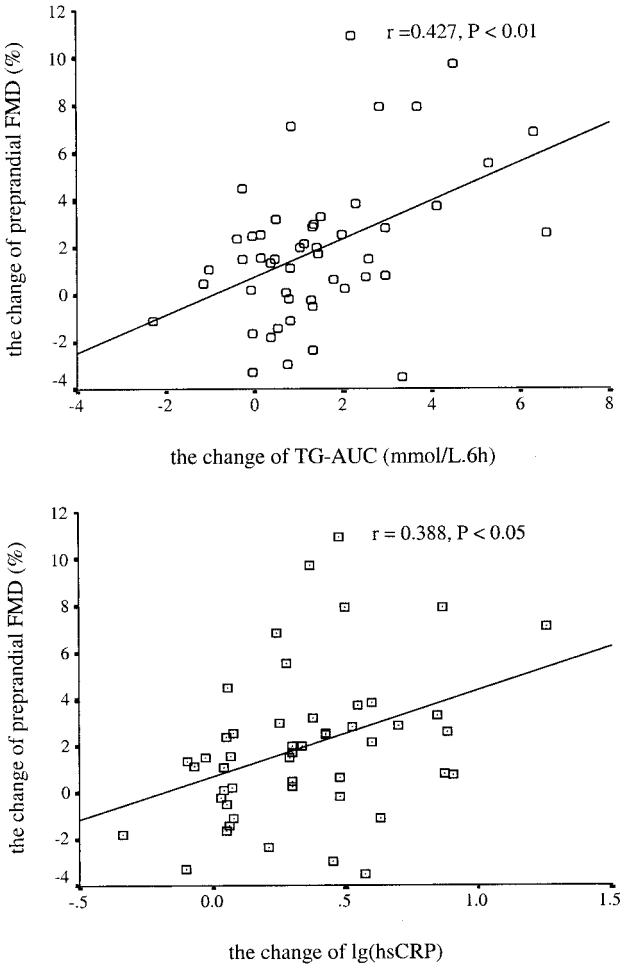

Figure 4. Correlations between change in preprandial FMD and changes in TG-AUC and log(hs-CRP) after 6-week xuezhikang treatment in all CHD patients.

Discussion

The postprandial state plays a critical role in atherogenesis. Acutely impaired endothelium-dependent vasodilation after a high-fat meal has been found to be associated with postprandial hypertriglyceridemia.[2,13,14] Furthermore, postprandial hypertriglyceridemia may induce endothelial dysfunction through the direct effects of triglyceride-rich lipoproteins[3,4] and increasing oxidative stress in circulation.[1,15,16] These data indicate that lowering postprandial triglyceride concentration may lead to improvement of endothelial function.

In this randomized, placebo-controlled study, we showed that xuezhikang, an extract of Cholestin, significantly decreased postprandial triglyceride concentrations. Furthermore, patients in the xuezhikang group were protected from postprandial endothelial dysfunction, as measured by FMD. In addition, xuezhikang led to a significant reduction in the inflammatory marker hs-CRP.

The effect of lipid-lowering treatment on endothelial function has been controversial. Fibrates improved postprandial endothelial function in type 2 diabetes.[17] However, this effect was not observed in healthy subjects,[14] even though postprandial hypertriglyceridemia was attenuated and fasting FMD was improved.[18] Recently, evidence showed that statins reduced remnant-like particles–cholesterol[14] and serum triglyceride[15] after an oral fat load. In addition, statin therapy attenuated postprandial endothelial dysfunction in healthy volunteers and in diabetic patients.[14,15] Because xuezhikang contains statin-like components, similar results were observed in our study. Xuezhikang decreased postprandial hypertriglyceridemia and protected preprandial and postprandial endothelial function. These data support the hypothesis that xuezhikang improves endothelial function by eliminating triglyceride-rich lipoprotein and other harmful factors associated with postprandial hypertriglyceridemia. Furthermore, xuezhikang may exert a direct protective effect on endothelial cells and maintain nitric oxide bioactivity by its antioxidant properties.[19]

Endothelial dysfunction is closely related to systemic inflammation in addition to dyslipidemia. Postprandial hypertriglyceridemia can activate nuclear factor-κB by postprandial triglyceride-rich lipoproteins.[20–22] Therefore, repeated postprandial hypertriglyceridemia could conceivably lead to a chronic inflammatory state, which can contribute further to endothelial dysfunction. For example, CRP, a marker and a mediator of inflammation, directly inhibits the activity and expression of endothelial nitric oxide synthase[23] and increases endothelin-1 expression[24] in endothelial cells. In previous studies, CRP concentration was an independent predictor for endothelium-dependent vasodilation in patients with coronary artery disease[25] and in healthy children.[26] Furthermore, children with higher

CRP levels have worse endothelial function as assessed by FMD.[26] Interestingly, reducing CRP levels over time is associated with improvement of endothelium-dependent vasodilation in patients with coronary artery disease.[25,27] In this study, xuezhikang had a potent effect on lowering CRP, which was associated with improvement of fasting FMD. This supports the hypothesis that xuezhikang may protect endothelial function partly through an antiinflammatory mechanism. It is known that statins exert potent antiinflammatory effects independent of their lipid-lowering properties. Xuezhikang contains naturally occurring statin-like elements. Nevertheless, we found a significant correlation between the reductions of hs-CRP and TG-AUC in the xuezhikang group. Therefore, the reduction in hs-CRP levels observed in this study could be secondary to decreased postprandial triglyceride levels as well as the direct antiinflammatory effect of xuezhikang.

Patients in the placebo arm also had a mild reduction in CRP concentration. Patients in this arm received dietary control and other agents such as aspirin, nitrates, metoprolol, and fosinopril. Although a low dose (80 mg/d) of aspirin, which is near the dose of aspirin in the present study, seemed to have no effect on CRP levels in healthy volunteers,[28] β-blockers and angiotensin-converting enzyme inhibitors inhibit cytokines synthesis and lower CRP concentration effectively in patients with CHD.[29–31] Furthermore, a low-energy diet could reduce vascular inflammatory factors, including CRP.[32] Therefore, the reduction seen in CRP levels in the placebo arm could be related to dietary control and the combination of medications these patients were taking.

Although a small decrease in CRP levels were seen in the placebo arm, FMD did not improve in these patients. Previous studies have shown that aspirin at moderate doses (162 mg/d) for 8 weeks effectively restores endothelium-dependent dilation in hypertensive patients[33]; however, a lower dose of aspirin (100 mg/d for 6 weeks) seemed to be ineffective in the same population. In our study, patients received low-dose aspirin, which could explain the lack of improvement in FMD in the placebo group. Furthermore, compared with previous studies, our patients were a sicker group of patients with multiple coronary risk factors.

In summary, xuezhikang significantly decreased hs-CRP levels in addition to its lipid-lowering effects. Furthermore, xuezhikang significantly improved FMD during preprandial and postprandial states. Taken together, these results suggest that xuezhikang protects endothelial function through its potent systemic antiinflammatory and lipid-lowering effects. Future large randomized trials are needed to examine the protective effects of xuezhikang in preventing cardiovascular events.

Acknowledgments

This study was supported in part by WBL Peking University Biotech Co, Ltd, China. We thank all subjects who participated in this study; Drs Dahan Tang and HaiQiu Wu for their useful comments and support regarding the nutrition design; Dr Ming Hu for serum lipids and hs-CRP measurements; and the Department of Clinical Laboratory, Second Xiangya Hospital, for their assistance.

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