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Changes in serum interleukin-6 and high-sensitivity C-reactive protein levels in patients with acute coronary syndrome and their responses to simvastatin

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Abstract The role of inflammation in acute coronary syndrome (ACS) and the mechanism by which statin treats ACS is explored. Serum high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) levels were measured in 50 patients with ACS [including 30 cases with unstable angina (UA) and 20 patients with acute myocardial infarction (AMI)], 34 patients with stable angina (SA), and 30 controls. Patients in the ACS group were randomly assigned to a simvastatin group (including a simvastatin AMI subgroup, $n = 11$ and a simvastatin UA subgroup, $n = 14$) and a routine group (including a routine AMI subgroup, $n = 9$ and a routine UA subgroup, $n = 16$). The simvastatin group was given simvastatin 20 mg/day and the routine group a placebo. After a 3-week follow-up, serum hs-CRP, IL-6 levels, and serum lipid concentrations were measured again. Both serum IL-6 and hs-CRP levels were significantly higher in the ACS group (including the UA and AMI subgroups) than in the SA and control groups ($P < 0.001$). After 3 weeks of treatment with simvastatin, the serum IL-6, hs-CRP, total cholesterol, and low-density lipoprotein cholesterol levels were decreased significantly in the simvastatin group ($P < 0.001$), but no significant changes were observed in the routine group. No relationship was observed between the rate of decrease of serum IL-6 or hs-CRP and serum lipids levels. The hs-CRP level showed a significant correlation with IL-6 by Spearman's rank correlation analysis ($P < 0.01$). Inflammation plays an important role in the initiation of ACS. Simvastatin possesses an anti-inflammatory effect, independent of its lipid-lowering action, which may play an important role in the early treatment of ACS.

Key words Acute coronary syndrome · Interleukin-6 · High-sensitivity C-reactive protein · Inflammation · Simvastatin

Introduction

Advances in the etiology and pathogenesis of coronary heart disease (CHD) have shown it to be a chronic low-grade inflammatory disease. Nowadays, accumulating evidence has revealed that inflammation plays an important role in the initiation, progression, and even in the occurrence of complications of atheroscleroses (AS).[1] Inflammation affects the stability of atheromatous plaque and facilitate its rupture, and acute coronary syndrome (ACS) is caused by thrombosis secondary to the rupture of plaque.[2] Some studies suggest that a series of inflammatory cells and factors may take part in the process of AS and ACS.[3] Numerous studies showed a dose–response relationship between the level of high-sensitivity C-reactive protein (hs-CRP) and the risk of a coronary incident[4] and recurrent coronary events,[5] while other observations revealed similar results with interleukin-6 (IL-6).[4–6] Recently, statin has been considered to be an anti-inflammatory agent independent of its lipid-lowering action; therefore, it can decrease the rate of coronary events and improve the prognosis.[7,8] However, the results of interventions in ACS with statin are not identical, and the mechanism is still not fully known. The novelty of our study is the early intervention with statin in ACS, which has only been attempted by a few investigators, especially in China.

Materials and methods

Subjects

This study included 106 patients who were hospitalized at the Department of Cardiology of the Second Xiangya Hospital for chest pain syndrome between March and August

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2002. They had a diagnosis of definite AMI or UA (including initial onset angina pectoris, progressive angina pectoris, and spontaneous angina pectoris) or SA according to the nomenclature and criteria for the diagnosis of ischemic heart disease reported by the ISFC/WHO in 1979. Patients with acute infection or wounds or who had undergone surgery within the previous 4 weeks, those with cerebral vascular accident, peripheral vascular disease, liver or renal insufficiency, malignant tumor, chronic connective tissue diseases and immune disease, or those who had taken statin 4 weeks prior to hospitalization, were excluded from the study. In all, 84 patients fulfilled the criteria. On the basis of their diagnoses they were classified into the ACS group ($n = 50$), including an AMI subgroup ($n = 20$) and UA subgroup ($n = 30$), or the SA group ($n = 34$). Thirty healthy subjects who were among health examinees at an outpatient clinic and in whom cardiac and other organic diseases were eliminated by ECG, liver, renal function, and other tests, were enrolled in the normal control group (NC).

Blood samples

In each patient, 3 ml blood was drawn by venipuncture between 06:00 and 07:00 h after fasting for 12 h on the second day of hospitalization in the ACS and SA groups and on the day of examination in the control group. Blood samples were collected in plastic tubes and the serum was separated by centrifugation at 4°C for 15 min at $3000 \times g$, then frozen and stored at −70°C for future use. Patients in the ACS group were randomly and single-blindedly assigned to a simvastatin group (including the simvastatin AMI subgroup, $n = 11$, and the simvastatin UA group, $n = 14$) and a routine group (including the routine AMI group, $n = 9$, and the routine UA group, $n = 16$). From the second day after hospitalization, the routine group received placebo and the simvastatin group was given 20 mg of simvastatin per day as routine therapy (including nitrate, aspirin, β-blocker, and angiotensin-converting enzyme inhibitor). After an average 3-week follow-up, serum hs-CRP, IL-6, and serum lipid levels were measured again.

Laboratory methods

The concentration of serum IL-6 was determined by enzyme-linked immunosorbent assay (serum IL-6 ELISA kit, Jingmei Engineering, China). The level of serum hs-CRP was measured by the particle-enhanced immunoturbidimetric method (Orion Diagnostica, Espoo, Finland). Serum total cholesterol (TC), triglyceride (TG), and fasting blood sugar (FBS) were detected by enzymatic methods; high-density lipoprotein cholesterol (HDL-C) was determined by the polyanion polymer/detergent assay (PPD), and LDL-C by the surfactant LDL-C assay (SUR). White blood cells (WBC) were counted by the System of Automated Cell Analysis.

Statistical methods

All of the statistical analyses were done with the software package SPSS10.0 (SPSS, Chicago, IL, USA). Results are expressed as mean ± standard deviation. Continuous variables were compared using the one-way analysis of variance (ANOVA) test or student's *t*-test, and categorical variables were compared using the Kruskal-Wallis test. Associations between serum levels of IL-6 and hs-CRP as well as cardiovascular risk factors were estimated by Spearman's rank correlation analysis. Two-tailed values of probability of less than 0.05 were considered statistically significant.

Ethical considerations

Prior to participating in the study, the protocol of which was approved by the Ethics Committee of Hunan, all patients and controls gave their informed consent.

Results

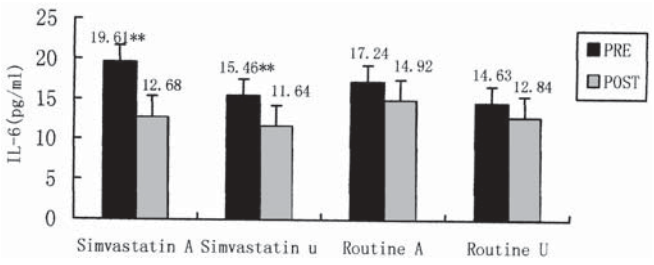
A total of 50 ACS (UA, 30; AMI, 20) patients, 34 SA patients, and 30 controls were included. Table 1 summarizes the basic characteristics of patients and controls, and no significant differences in age, sex, BMI, past history of hypertension and diabetes, drug-taking and smoking existed among the groups.

Serum levels of IL-6 and hs-CRP were significantly higher in the ACS group than in the SA and NC groups ($P < 0.001$), but no significant difference in IL-6 and hs-CRP was observed between the SA and NC groups ($P > 0.05$). Compared with the UA subgroup, and the SA and NC groups, the AMI subgroup showed significantly higher levels of serum IL-6 and hs-CRP ($P < 0.001$) and in a comparison with the SA and NC groups, the UA subgroup also showed significantly higher levels of serum IL-6 and hs-CRP ($P < 0.05$) (Table 2).

No significant difference in age, sex, BMI, smoking, past history of hypertension and diabetes, and the levels of serum IL-6, hs-CRP, and lipids existed between the routine group and the simvastatin group, or among all the subgroups before treatment with simvastatin ($P > 0.05$) (Table 3).

After a 3-week treatment with simvastatin, the serum IL-6 and hs-CRP levels were both significantly decreased in the simvastatin group (including the simvastatin AMI and simvastatin UA subgroups) ($P < 0.001$) but not in the routine group (including the routine AMI and UA groups) ($P > 0.05$). There was a significant difference in the rate of decrease in the serum IL-6 and hs-CRP levels between the simvastatin AMI and routine AMI groups, and between the simvastatin UA and routine UA groups ($P < 0.05$). The rate of decrease in serum hs-CRP and IL-6 concentrations was significantly positively correlated ($r = 0.431$, $P < 0.05$) (Fig. 1).

With simvastatin intervention, the levels of TC and LDL-C declined significantly in the simvastatin groups (in-



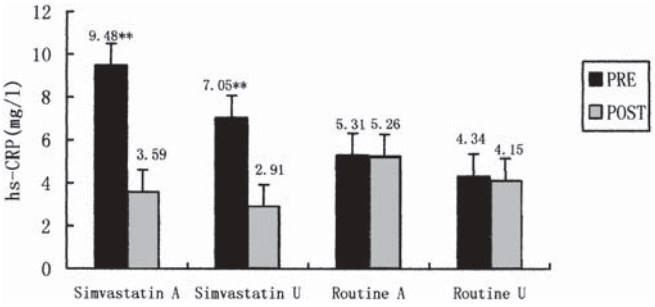


Fig. 1. Levels of serum interleukin-6 (*IL-6*) and high-sensitivity C-reactive protein (*hs-CRP*) before and after intervention with simvastatin. PRE, pretreatment; POST, post-treatment. *Simvastatin A*: acute myocardial infarction (AMI) subgroup of simvastatin group; *Simvastatin U*: unstable angina (UA) subgroup of the simvastatin group; *Routine A*: AMI subgroup of the routine group; *Routine U*: UA subgroup of the routine group. The paired *t*-test was used for comparison between before and after treatment with simvastatin. **In the simvastatin group, the serum IL-6 and hs-CRP levels significantly declined after intervention with simvastatin ($P < 0.01$)

Table 1. Basic characteristics of patients and controls

	ACS ($n = 50$)		SA ($n = 34$)	NC ($n = 30$)	*P*
	UA ($n = 30$)	AMI ($n = 20$)			
Age (years)	65.7 ± 8.3	65.1 ± 9.7	62.6 ± 9.7	61.3 ± 6.9	0.098
Sex					
Male	23	15	22	20	0.693
Female	7	5	12	10	
BMI (kg/m^2)	23.7 ± 2.7	23.3 ± 2.8	23.2 ± 2.4	24.1 ± 2.7	0.453
Smoking (cigarettes/day)					
0	10	6	21	16	0.851
≤14	10	8	6	7	
15–24	6	5	6	6	
≥25	2	3	1	1	
Past history					
Hypertension	15	12	17	8	0.239
Diabetes	1	3	1	0	0.101
Taking drugs					
ACEI	20	12	24	0	0.655[$]
β-Blocker	12	12	15	0	0.402[$]
Aspirin	25	17	25	0	0.782[$]
Nitrates	25	16	29	0	0.629[$]

The one-way analysis of variance (ANOVA) test was used for continuous variables and the Kruskal-Wallis test for categorical variables. No significant differences existed in age, sex, BMI, past history of hypertension and diabetes, and drug-taking and smoking among the groups
ACS, acute coronary syndrome group; UA unstable angina group; AMI, acute myocardial infarction group; SA, stable angina group; NC, normal control group. BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitor
[$] *P* values educed by comparing the mean of the UA and AMI subgroups to that of the SA group

Table 2. Levels of serum interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hs-CRP)

	IL-6 (pg/ml)	hs-CRP (mg/l)
ACS ($n = 50$)	19.55 ± 6.71**	11.22 ± 2.65**
AMI ($n = 20$)	21.88 ± 3.69**	24.61 ± 6.07**
UA ($n = 30$)	18.61 ± 1.77*	5.48 ± 0.59*
SA ($n = 34$)	13.04 ± 4.57	1.04 ± 0.35
NC ($n = 30$)	11.66 ± 2.44	1.21 ± 0.37

The one-way ANOVA test was used for comparison between groups
** Compared with the SA and NC groups, the ACS group showed a significant difference ($P < 0.001$)
** Compared with the UA subgroup, and the SA and NC groups, the AMI subgroup showed a significant difference ($P < 0.001$)
* Compared with the SA and NC groups, the UA subgroup showed a significant difference ($P < 0.05$)

cluding the simvastatin AMI and simvastatin UA subgroups) ($P < 0.05$) but not in the routine group (including the routine AMI and routine UA subgroups) ($P > 0.05$). No relationship was observed between the rates of decrease in serum IL-6 and TC or LDL-C levels, or between the rate of decrease in serum hs-CRP and TC or LDL-C levels ($P > 0.05$) (Table 4).

Serum IL-6 levels positively correlated with serum hs-CRP in all groups ($P < 0.01$). The serum hs-CRP and IL-6 levels both correlated positively with creative kinase (CK) and its MB isoenzyme (CKMB) concentrations in the AMI subgroup ($P < 0.01$), with smoking in the SA group, and with TC in the UA subgroup ($P < 0.05$). Moreover, hs-CRP correlated positively with systolic blood pressure (SBP) in

Table 3. Basic characteristics of the simvastatin group and the routine group

	Simvastatin group		Routine group		*P*
	UA	AMI	UA	AMI	
Cases	14	11	16	9	0.189
Age (years)	63.2 ± 4.2	65.7 ± 3.6	64.6 ± 7.3	67.4 ± 4.5	0.800
Sex					
Male	10	9	13	3	0.415
Female	4	2	3	3	
BMI (kg/m^2)	23.59 ± 3.23	22.54 ± 2.42	23.94 ± 2.54	22.91 ± 2.72	0.810
Smoking cigarettes/day					
0	6	3	4	3	0.247
1–14	5	3	8	2	
15–24	2	3	4	2	
≥25	1	2	0	2	
Past history					
Hypertension	7	6	9	5	0.856
Diabetes	1	1	0	2	0.971
IL-6 (pg/l)	17.28 ± 3.21	17.30 ± 3.10	13.64 ± 3.84	19.00 ± 3.02	0.152
hs-CRP (mg/l)	6.44 ± 3.90	10.25 ± 3.55	3.18 ± 2.35	7.36 ± 3.03	0.096
TC	4.62 ± 1.12	3.57 ± 1.04	4.19 ± 1.00	4.55 ± 0.54	0.847
LDL-C	2.26 ± 0.72	2.48 ± 0.78	2.41 ± 0.75	3.07 ± 0.79	0.515
HDL-C	1.00 ± 0.20	1.27 ± 0.23	1.10 ± 0.30	0.98 ± 0.24	0.947
TG	1.35 ± 0.65	1.87 ± 0.79	1.67 ± 0.78	0.94 ± 0.69	0.676

The one-way ANOVA test was used for continuous variables and the Kruskal-Wallis test was used for categorical variables. There were no significant differences in age, sex, BMI, smoking, past history of hypertension and diabetes, and serum levels of IL-6, hs-CRP, and lipids between the routine group and the simvastatin group, or among all subgroups before treatment with simvastatin ($P > 0.05$)
AMI, acute myocardium infarction; UA, unstable angina; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides

Table 4. Correlation coefficients between serum levels of IL-6, hs-CRP, and other cardiovascular risk factors of coronary heart disease

	IL-6				hs-CRP			
	ACS		SA	NC	ACS		SA	NC
	AMI	UA			AMI	UA		
IL-6	1.000	1.000	1.000	1.000	0.529**	0.462**	0.497**	0.764**
hs-CRP	0.529**	0.462**	0.497**	0.764**	1.000	1.000	1.000	1.000
Age (years)	0.428*	0.052	0.098	0.139	0.105	0.014	0.025	0.039
Sex	0.230	0.031	0.050	0.268	0.290	0.184	−0.300	0.249
Smoking	0.354	0.378*	0.359*	0.231	0.131	0.120	0.412*	0.167
BMI	0.166	−0.013	0.129	0.017	0.350	0.019	0.212	0.152
SBP	−0.88	0.171	0.132	0.374	−0.055	0.363#	−0.053	0.387#
DBP	0.239	0.144	0.110	0.110	0.247	0.277	−0.025	0.078
TC	−0.046	0.321*	0.085	0.179	−0.177	0.463*	0.054	0.396#
LDL-C	0.038	0.035	0.150	0.244	−0.067	0.243	−0.039	0.385#
HDL-C	0.125	−0.068	0.048	−0.087	0.029	−0.118	−0.205	−0.126
HDTC	0.079	−0.029	0.078	0.102	0.087	−0.256	−0.294	−0.212
TG	−0.319	0.157	0.193	0.089	0.257	−0.112	0.409#	0.284
CK	0.493**	0.218	0.042	–	0.400**	−0.089	−0.167	–
CKMB	0.688**	0.310*	0.067	–	0.537**	0.128	−0.106	–
CAG	−0.253	0.143	−0.152	–	−0.298	0.288	0.313	–
WBC	0.231	0.036	0.136	0.158	0.389#	0.163	0.211	0.240
FBS	−0.097	−0.203	0.145	0.214	0.282	−0.047	0.099	0.367#

Values are expressed as Spearman rank correlation coefficients
BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HDTC, HDL-C/TC; TG, triglycerides; CK, creatine kinase; CKMB, MB isoenzyme of creatine kinase; CAG, coronary arteriography; WBC, white blood cells; FBS, fasting blood sugar
** The serum hs-CRP and IL-6 levels positively correlated with each other in all groups, and positively correlated with CKMB and CK in the AMI subgroup ($P < 0.01$)
* The serum hs-CRP and IL-6 levels both correlated positively with TC in the UA subgroup, with smoking in the SA group ($P < 0.05$)
The serum IL-6 level also correlated positively with smoking in the UA subgroup, with age in the AMI subgroup and with CKMB in the UA subgroup
hs-CRP correlated positively with SBP in the AMI subgroup and the CN group, with WBC in the AMI subgroup, TG in the SA group, and with TC, LDL-C, and FBS in the NC group ($P < 0.05$)

the AMI subgroup and the NC group, to WBC in the AMI subgroup, to TG in the SA group, and to TC, LDL-C, and FBS in the NC group ($P < 0.05$), and the serum IL-6 level also correlated positively with smoking in the UA subgroup, with age in the AMI subgroup, and with CKMB in the UA subgroup ($P < 0.05$); however, no significant correlation was observed between the levels of serum hs-CRP or IL-6 and sex, BMI, and the number of vessels involved by AS (stenosed area ≥50% lumen area under coronary arteriography).

Discussion

Interleukin-6 is a multifunctional proinflammatory factor secreted by activated monocytes, macrophages, T lymphocytes, endothelial cells, and fibroblasts. After binding to a receptor, IL-6 can activate tyrosine protein kinase (TPK) via glycoprotein 130 (gp130). Activated TPK activates serine or threonine protein kinase, which in turn accelerates related gene transcription, and leading to the final effect. Besides stimulating the liver to develop acute phase reactants (including CRP, fibrinogen, etc.), IL-6 also induces T lymphocytes to proliferate, differentiate, and release cytokine, and facilitates B lymphocytes to proliferate, differentiate, and develop antibodies, thereby taking part in the inflammation process.[2] C-reactive protein is one of the acute inflammatory markers synthesized by the liver which not only reflects the activity of upper stream inflammatory factors, but also activates complement, induces adhesion molecules and tissue factors to express, accelerates the uptake of lipids by endothelial cells and macrophages, secretes matrix metalloproteinase, and recruits macrophages to blood vessels.[2] The present study showed that the levels of serum hs-CRP and IL-6 were both obviously higher in the ACS group (including the AMI and UA subgroups) compared with the SA and NC groups. These results are in accordance with the report by Yu et al.[9] and suggest that inflammation may play an important role in ACS. After a 3-week treatment regime with simvastatin, serum TC and LDL-C concentrations as well as serum hs-CRP and IL-6 levels were significantly decreased in the simvastatin group. However, no correlation was observed between the rates of decrease in serum lipid levels and the serum hs-CRP or IL-6 levels. These results are similar to those of studies performed in other countries.[8] Just as the PRINCE study showed, our finding also revealed that statin possesses an anti-inflammatory effect that is independent of its lipid-lowering action.[7–8] The mechanism of the anti-inflammatory effect of statin is not yet completely understood. However, animal experiments showed that statin can reduce the quantity of macrophages, and suppress the expression and activity of tissue factors, matrix metalloproteinase, and adherent molecules in atheroma.[10] In vitro studies also demonstrated that statin could repress macrophages, adipose cells, and endothelial cells to release proinflammatory factors.[11] These results support the early use of statin so it can quickly inhibit the inflammatory reaction and improve the prognosis.

Positive correlations were noted not only between serum hs-CRP and the IL-6 levels in all three groups, but also between the rate of decrease in serum hs-CRP and IL-6 with simvastatin intervention. As it is one of the proinflammatory factors, IL-6 can induce the liver to yield CRP. Thus when the coronary artery is damaged and inflammation occurs, the IL-6 concentration is elevated which induces a secondary increase in CRP. After intervention with statin, owing to its anti-inflammatory effect, the level of IL-6 decreases, thus leading to the decline in the level of CRP. This is probably the reason for the correlation between IL-6 and hs-CRP levels, and between the rate of decrease in IL-6 and hs-CRP. Our study also showed that the serum hs-CRP and IL-6 levels were significantly higher in the AMI subgroup than in the UA subgroup and that they were positively correlated with the CKMB and CK concentrations in the AMI subgroup, thus suggesting that the serum levels of hs-CRP and IL-6 are correlated with the degree of myocardial injury and necrosis. However, the levels of serum IL-6 and hs-CRP were significantly higher in the UA subgroup than in the SA and CN groups, and partial correlation analysis also showed that the diagnosis still correlated positively with hs-CRP ($r = 0.285$, $P = 0.045$) and IL-6 ($r = 0.348$, $P = 0.037$) after controlling the effect of CKMB. This suggests that the rise in the serum levels of hs-CRP and IL-6 in ACS is not only the result of the injury to the myocardium but also is caused by inflammation. There are data showing that in ACS, hs-CRP predicts recurrent myocardial infarction independent of troponins, which suggests it is not merely a marker for the extent of myocardial damage.[11] Moreover, the serum hs-CRP and IL-6 levels both correlated positively with TC in the UA subgroup and to smoking in the SA group; while the serum IL-6 level also correlated positively with smoking in the UA subgroup, to age in the AMI subgroup, and to CKMB in the UA subgroup, hs-CRP was also positively related to SBP in the AMI subgroup and the CN group, to TG in the SA group, and to TC and LDL-C in the NC group. These results suggest that some of the usual risk factors of CHD (such as the heightened TC, LDL-C, and TG levels and SBP, etc.) may cause coronary atherosclerosis, and even coronary events mediated by local inflammation.

Conclusions

Inflammation plays an important role in the initiation of ACS. Simvastatin possesses an anti-inflammatory effect independent of its lipid-lowering action, and this anti-inflammatory effect may play an important role in the early treatment of ACS. As a small number of samples were used in this study, the results of this experiment need to be tested further by more studies.

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