

Depressed Inflammatory Response to Repeated Angioplasty in Unstable Angina Patients with an In-Stent Restenosis

Sang-Jin Han, MD, Young-Cheoul Doo, MD, Goo-Yung Cho, MD, Kyung-Soon Hong, MD, Kyoo-Rok Han, MD, Nam-Ho Lee, MD, Dong-Jin Oh, MD, Kyu-Hyung Ryu, MD, Chong-Yun Rim, MD, Kwang-Hahk Lee, MD and Yung Lee, MD

Division of Cardiology, Department of Internal Medicine, Kang-Dong Sacred Heart Hospital, College of Medicine, Hallym University, Seoul, Korea

ABSTRACT

Background: Inflammation plays a key role in the pathogenesis of an in-stent restenosis because it promotes neointimal proliferation. This study was performed to determine responses of the C-reactive protein (CRP) in unstable angina patients with an in-stent restenosis undergoing repeated percutaneous transluminal coronary angioplasty (re-PTCA). **Methods:** The study subjects (unstable angina) were classified into 2 groups: Group A (n=30, 15 men, mean age 62 years) had a re-PTCA for an in-stent restenosis lesion and Group B (n=60, 33 men, mean age 63 years) underwent a stent implantation for a *de novo* lesion. **Results:** The baseline CRP levels in group A were significantly lower than in group B, as well as 6 and 24 hours after intervention. Twenty four hours after intervention, the CRP levels increased (>4 mg/L) in 3 out of 30 patients (10%) of group A but increased in 32 out of 60 patients (53%) in group B ($p<0.001$). The differences in the CRP levels between the baseline and 24 hours after intervention were significantly lower in group A than in group B (0.8 and 2.15 mg/L, respectively, $p<0.001$). In group B, the serum CRP levels 24 hours after intervention were significantly higher than the baseline levels ($p<0.05$), but not in group A. **Conclusions:** The CRP expression level is significantly lower in unstable angina patients undergoing a re-PTCA for an in-stent restenosis than those undergoing a stent implantation for a *de novo* lesion. (Korean Circulation J 2004;34(1):41-46)

KEY WORDS: C-reactive protein; Coronary restenosis; Stents; Angioplasty.

Introduction

The C-reactive protein (CRP) levels are powerful predictors of cardiac complications in patients with unstable angina,¹⁻³⁾ and have been reported to be predictive of a restenosis after a balloon angioplasty or a stent implantation.⁴⁻¹⁰⁾ However, there is a paucity of data concerning the clinical implications of inflammation in patients with an in-stent restenosis undergoing repeated percutaneous

transluminal coronary angioplasty (re-PTCA). This study was performed to determine changes in the CRP levels before and after a re-PTCA in patients with an in-stent restenosis.

Methods

Subjects

From April 2001 to May 2002, percutaneous coronary intervention was performed on 285 consecutive patients (unstable angina; 160 patients). A total of 132 patients, who presented with unstable angina were subjected to serial laboratory testing, which included measuring the CRP and cardiac enzyme levels, were enrolled in this study. The patients were divided into three groups according to the clinical circumstances of their acute

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Correspondence : Young-Cheoul Doo, MD. Division of Cardiology, Department of Internal Medicine, Kang-Dong Sacred Heart Hospital, College of Medicine, Hallym University, #445, Gildong, Kangdong-gu, Seoul 134-010, Korea
Tel : 82-2-2224-2649, Fax : 82-2-478-6925
E-mail : ycdoo97@hallym.or.kr

ischaemic episode and the severity of the ischemia i.e. a new onset or accelerating primary angina without resting pain (unstable angina IB), primary angina at rest within the past month but not within the preceding 48 hours (unstable angina IIB), and primary angina at rest within the previous 48 hours (unstable angina IIIB).¹¹⁾ Patients with concomitant inflammatory disease (n=10), cancer (n=2), or current infection (n=9), and cases of rotational atherectomy (n=5) were excluded. Patients who developed non-Q (Creatine kinase \geq three times the upper normal limit, with a concomitant rise in MB isoenzyme) (n=6), Q wave myocardial infarction (n=3), or severe local hematoma requiring transfusion after intervention (n=7) were also excluded. Therefore, 90 patients were included in the study.

The 90 study subjects were classified into 2 groups: Group A (n=30, male 15, mean age 62 years) received a re-PTCA for an in-stent restenosis lesion and Group B (n=60, male 33, mean age 63 years) received a coronary stent implantation for a *de novo* lesion.

The study was revised and approved by the Institution's Ethics Committee, and all eligible patients provided written informed consent.

Design of the study

Blood samples were taken prior to the intervention, and 6, 24, and 72 hours after the intervention to assess the serum CRP and cardiac enzyme levels. The serum CRP concentrations were measured in a single batch at the end of the study. All the patients received 200 mg aspirin once per day and 250 mg ticlopidine twice per day before the intervention. In addition, before the intervention, heparin was given as an intravenous bolus of 8,000 to 10,000 units and then additional heparin, as required, was administered to maintain an activated clotting time of ≥ 250 sec. Coronary angiography and percutaneous coronary intervention were performed using the standard technique in all patients. The coronary interventions were performed via the radial artery, except for 20 cases. Two interventional cardiologists who were blinded to the CRP results read each coronary angiogram.

Laboratory assays

CRP was measured using rate nephelometry (IMMAGE[®] Immunochemistry system, Beckman Coulter, Inc., Fullerton, CA, USA). This CRP analytical range was 0.1 to 96 mg/L (normal values < 8 mg/L). The creatine kinase (CK) activities were measured using the GSOC method (Synchron CX[®] 4 System, Beckman Inc, California, USA). The serum troponin-T level was measured by competitive electrochemiluminescence using a reagent purchased from Boehringer Mannheim (Elevys 1010, Boehringer Mannheim). The normal CK values ranged from 22 to 269 IU/L. The upper limit of the normal range for the cardiac troponin-T was 0.1 ng/mL.

Statistical analysis

Nonparametric tests were used because the CRP data were not normally distributed. The CRP values are expressed as a median and a range. CK and troponin-T are expressed as a mean \pm SD. The continuous variables were compared using a Wilcoxon Signed Ranks test (CRP) and either an unpaired or a paired Student's *t* test (CK and troponin-T). A chi-square test was used to compare the discrete variables. A $p < 0.05$ was considered significant.

Results

Baseline characteristics of subjects

The baseline clinical and angiographic characteristics are shown in Table 1. The post-intervention minimal luminal diameter (MLD) was significantly higher in group B (stent implantation in *de novo* lesion, 3.2 ± 0.5 mm) than in group A (2.7 ± 0.4 mm, $p < 0.05$). Other variables, such as gender, age, risk factors for coronary artery disease, medications, and multi-vessel disease were similar in the two groups (Table 1).

CRP and cardiac enzymes

The baseline serum CRP levels were significantly lower in group A (in-stent restenosis) than in group B (2.32 and 3.50 mg/L, respectively, $p < 0.001$). The serum

Table 1. Clinical and angiographic characteristics of the subjects

	Group A (n=30 patients)	Group B (n=60 patients)
Age (years)	62± 9	63± 9
Men/women	15/15	33/27
Systemic hypertension	16 (53%)	42 (70%)
Diabetes mellitus	5 (15%)	22 (37%)
Hypercholesterolemia (total cholesterol >220mg/L)	12 (40%)	32 (53%)
Smoking	12 (40%)	17 (28%)
Ejection fraction (%)	60±10	60±9
Braunwald Class of UA IB/IIIB/IIIB	17/10/3	25/24/11
Type of in-stent restenosis focal/diffuse/proliferative	8/17/5	
Admission medication		
Aspirin	26 (87%)	48 (80%)
Beta-blockers	11 (37%)	24 (40%)
Statins	14 (45%)	25 (42%)
Multi-vessel disease	11 (38%)	31 (52%)
Major dissection	2 (5%)	4 (7%)
Lesion length (mm)	16.4±4.9	15.2±4.5
Reference diameter (mm)	3.2±0.4	3.3±0.5
Minimal luminal diameter (MLD)		
Pre-intervention (mm)	0.4±0.2	0.5±0.3
Post-intervention (mm)	2.7±0.4	3.2±0.5*

Age, ejection fraction, lesion length, and MLD are presented as mean±SD. UA: unstable angina, major dissection indicates type D, E, and F dissections, but there was no non-Q or Q wave myocardial infarction. *: p<0.05 vs. Group A

CRP levels 6 and 24 hours after intervention were also significantly lower in group A than in group B ($p<0.001$). Twenty four hours after the intervention, the CRP levels were higher (>4 mg/L) in only 3 out of 30 patients (10%) in group A but was higher in 32 out of 60 patients (53%) in group B ($p<0.001$). However, the serum creatine kinase and troponin-T levels were unchanged after the intervention in both groups (Table 2) (Figure 1, 2).

Differences in the CRP levels between the baseline and 24 hours after the intervention ($\Delta\text{CRP}_{24\text{h-baseline}}$), and the differences in the baseline and the maximum CRP levels after the intervention ($\Delta\text{CRP}_{\text{maximum-baseline}}$) in group A were 0.8 (-2.0 to 3.8) mg/L and 2.3 (-1.0 to 7.0) mg/L, respectively. These levels in group A were

significantly lower than in group B [$\Delta\text{CRP}_{24\text{h-baseline}}$: 2.15 (-3.0 to 20) mg/L, $p<0.001$, ($\text{CRP}_{\text{maximum-baseline}}$: 3.65 (-5 to 20) mg/L, $p<0.05$) (Table 2).

In group B, the serum CRP levels 24 hours after the intervention were significantly higher than the baseline ($p<0.05$), but not in group A ($p=\text{NS}$) (Table 2) (Figure 1). In group A, the CRP levels after the re-PTCA were unchanged regardless of the type of in-stent restenosis (focal, diffuse, or proliferative) (data not shown).

Discussion

Previous studies⁸⁾¹²⁻¹³⁾ have shown that in patients with unstable angina undergoing coronary artery stenting, most cardiac events are observed in those with high

Table 2. Serum CRP and cardiac enzyme levels before and after the intervention

	Group A (n=30 patients)	Group B (n=60 patients)
CRP (median, mg/L)		
Before intervention	2.32 (0.06–3.41) [†]	3.50 (0.06–11.7)
6 hrs after intervention	2.77 (0.06–8.00) [†]	4.45 (0.06–15.2)
24 hrs after intervention	3.02 (0.06–4.70) [†]	6.00 (0.06–22.3) [‡]
72 hrs after intervention	3.52 (0.06–7.87)	5.00 (0.06–21.0)
ΔCRP (mg/L)		
24 hrs-baseline	0.80 (–2.0–3.8) [†]	2.15 (–3.0–20.0)
72 hrs-baseline	2.00 (–2.0–7.0)	1.00 (–5.0–11.6)
Maximum-baseline	2.30 (–1.0–7.0)*	3.65 (–5.0–20.0)
At 24 hours after intervention		
CRP ≥4.0 mg/L	3 (10%) [†]	32 (53%)
CRP ≥8.0 mg/L	1 (3%)*	16 (27%)
Creatine kinase (IU/L)		
Before intervention	95±64	114±87
24 hrs after intervention	108±65	106±71
Troponin-T (ng/mL)		
Before intervention	0.07±0.05	0.08±0.05
24 hrs after intervention	0.11±0.05	0.09±0.05

The CRP levels are presented as a median and range. The creatine kinase and troponin-T level are presented as a mean±SD. ΔCRP_{maximum} (24 hrs or 72 hrs)-baseline indicates the difference between the maximal CRP level (at 24 or 72 hours after intervention) and the baseline CRP level. *: p<0.05, [†]: p<0.001 vs. Group B, [‡]: p<0.05 vs. before intervention

pre- or post-procedural serum CRP levels. Kornowski et al.¹⁴⁾ showed in an animal study that an inflammatory reaction plays an equally important role in neointimal formation after coronary stenting in cases of an arterial injury. However, there is insufficient data available to explain the clinical significance of CRP in patients with an in-stent restenosis undergoing re-PTCA. A recent study¹⁵⁾ reported that patients, with unstable angina caused by an in-stent restenosis, do not show a significant increase in the CRP level. However, Angioi et al.¹⁶⁾ reported that an increased CRP level at follow-up correlates with the presence of an in-stent restenosis, and suggested that inflammatory processes play an important role in the occurrence of an in-stent restenosis.

These results show that the CRP levels in patients with an in-stent restenosis undergoing re-PTCA are significantly lower than in patients with a stent implantation for a *de novo* lesion. In addition, no significant changes in the CRP levels were observed before and

after the re-PTCA in patients with an in-stent restenosis.

The precise mechanisms of the reduced CRP expression level in re-PTCA in patients with an in-stent restenosis are unknown. These responses may be due to the different plaque characteristics and/or the different individual susceptibility to inflammatory stimuli. *De novo* lesions usually consist of inflammatory cells with ruptured plaques, which are likely to be associated with a prominent increase in CRP after balloon injury. In contrast, in-stent restenosis lesions mainly consist of a neointimal hyperplasia, including the intercellular matrix, which contains smaller amounts of inflammatory cells. As a result, the baseline CRP level and the change in this level would be expected to be lower in in-stent restenosis lesions. Liuzzo et al.⁸⁾ reported that a plaque rupture per se is not the main cause of the increased CRP levels in unstable angina, and that an increased baseline CRP level is a marker of the hyper-responsiveness of the inflammatory system to even small stimuli. These

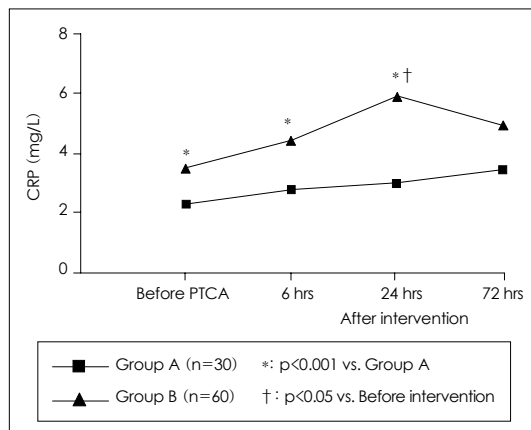


Figure 1. Trends of the CRP levels (median) of subjects. The median values of the CRP increased significantly in group B, peaking at 24 hours, but not in group A. The CRP levels at the baseline, and 6 and 24 hours after PTCA in group A were significantly lower than in group B. In group B, the CRP levels at 24 hours were significantly higher than the baseline, but the CRP levels were unchanged in group A. CRP: C-reactive protein, PTCA: percutaneous transluminal coronary angioplasty.

study results suggest that differences in the intrinsic characteristics of plaque might induce different inflammatory responses according to PTCA.

The results in this study contrast with those reported by Angioi et al.¹⁶⁾ The reason for this discrepancy is unknown. However, the changes in CRP levels were determined before and after rePTCA in patients with an in-stent restenosis and only involved patients who presented with unstable angina. Therefore, this study was more homogeneous, and provided a better opportunity for assessing the responsiveness of the inflammatory system to stimuli. Therefore, the present data might more reliably explain the clinical significance of the CRP in patients with an in-stent restenosis. However, the study results also need to be confirmed by a further study.

In this study, the CRP levels 72 hours after the re-PTCA were similar in the two groups, and the baseline CRP levels in group A were significantly lower than in group B. A previous study showed that the serum CRP levels usually peak 24 hours after PTCA and then decrease to the baseline within 48 to 72 hours after PTCA.⁸⁾ In group A, the CRP levels did not change significantly

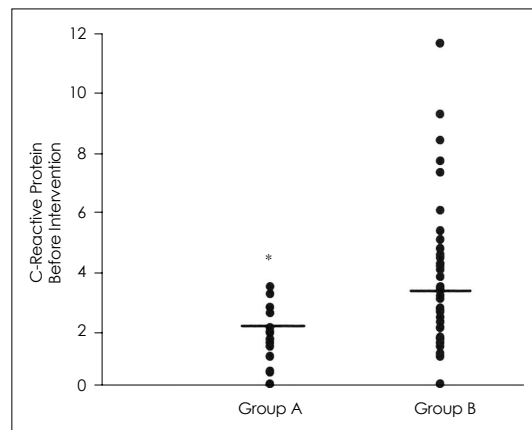


Figure 2. Distribution of the CRP levels (median) before the intervention in both groups (A and B). The CRP levels before the intervention in the group A were significantly lower than in the group B. *: $p < 0.001$.

as a result of re-PTCA. Therefore, the CRP levels 72 hours after PTCA could be similar in the two groups.

In conclusion, the CRP expression level was significantly lower in the unstable angina patients with re-PTCA for an in-stent restenosis than with a stent implantation for a *de novo* lesion.

Study limitations

The major limitation of this study was the small number of patients. Follow-up data, which was not presented in this study, should help clarify the prognostic implications of the reported findings.

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