Circ J 2005; **69:** 1477 – 1483

Elevated Preprocedural High-Sensitivity C-Reactive Protein Levels are Associated With Neointimal Hyperplasia and Restenosis Development After Successful Coronary Artery Stenting

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Background Recent data indicate that an elevated serum level of high-sensitivity C-reactive protein (hs-CRP) predicts the risk of recurrent coronary events, and that statin therapy decreases the risk of coronary events. This study assessed the relationship between the pre-procedural hs-CRP level and in-stent neointimal hyperplasia (NIH) after stenting and the effects of statins on the relationship between restenosis after stenting and the serum hs-CRP levels of patients with coronary artery disease.

Methods and Results This study included 100 patients who underwent stent implantation for angiographically significant stenosis. Patients were divided into a normal C-reactive protein (CRP) group (<0.5 mg/dl, n=59) and elevated CRP group (≥0.5 mg/dl, n=41). All patients underwent angiographic and intravascular ultrasound follow-up at 6 months. The baseline CRP level was 0.29±0.08 mg/dl in the normal CRP group and 2.90±2.31 mg/dl in the elevated CRP group. The NIH cross-sectional area (CSA) in the minimal lumen CSA at follow-up was significantly larger in the elevated CRP group compared with the normal CRP group (1.9±1.3 mm^2 vs 3.0±1.5 mm^2, p=0.001). A significant positive correlation was found between pre-interventional CRP level and NIH area (r=0.52, p<0.001). In patients with normal CRP, an association between statin therapy and restenosis was not observed. However, when the analysis was confined to patients with elevated CRP, statin therapy significantly reduced the restenosis rate (20% vs 37.5%, p=0.031). In the normal CRP group, the intra-stent neointimal area at 6 months was not different between the non-statin and statin groups (2.2±1.4 mm^2 vs 1.8±1.1 mm^2). However, in the elevated CRP group, statin therapy significantly decreased the neointimal area at 6-month follow-up (3.6± 1.7 mm^2 vs 2.4±1.3 mm^2, p<0.001).

Conclusion Measuring the pre-interventional hs-CRP level may help predict the development of restenosis after stenting and statin therapy will significantly reduce the restenosis rate in patients with an elevated hs-CRP. (*Circ J* 2005; **69:** 1477 – 1483)

Key Words: Inflammation; Restenosis; Stent

Inflammation plays an important role in both atherogenesis and atherothrombotic events[1] and high-sensitivity C-reactive protein (hs-CRP) has been associated with metabolic syndrome[2] and with increased risk for coronary artery disease (CAD).[3] Measurement of hs-CRP has been recommended for some patients to refine risk assessment[4] because hs-CRP levels have been shown to provide additional predictive information beyond traditional risk factors such as low-density lipoprotein cholesterol (LDL-C).[5] Increased hs-CRP levels may also be useful for identifying patients with low LDL-C who are at increased CAD risk and may benefit from statin therapy.[6]

Multiple large-scale clinical trials have shown that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (or statins) lower the mortality and morbidity in CAD and other atherosclerotic vascular diseases.[7–10] Treatment with statins, which have an anti-inflammatory effect and reduce C-reactive protein (CRP) levels, has been shown to decrease the risk of coronary events.[6]

To the best of our knowledge, however, few in vivo studies have dealt with the relationship between in-stent neointimal hyperplasia (NIH) and elevated CRP in patients with CAD. Therefore, we investigated this using intravascular ultrasound (IVUS) after successful stent implantation. We also examined the effects of statins on the relationship between the occurrence of restenosis after percutaneous coronary intervention (PCI) and inflammation by measuring the serum CRP levels of patients with CAD.

(Received June 13, 2005; revised manuscript received September 12, 2005; accepted September 22, 2005)

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Table 1 Demographic, Clinical and Laboratory Characteristics of the Patients With CAD

	Normal CRP (n=59)	*Elevated CRP (n=41)*	*p value*
hs-CRP (mg/dl)	*0.29±0.08*	*2.90±2.31*	*<0.001*
Age (years)	*54.4±10.6*	*57.8±10.8*	*NS*
Male	*43 (73%)*	*29 (71%)*	*NS*
Diabetes	*8 (14%)*	*8 (20%)*	*NS*
Hypertension	*28 (48%)*	*23 (56%)*	*NS*
Hyperlipidemia	*9 (15%)*	*8 (20%)*	*NS*
Smoking	*31 (53%)*	*23 (56%)*	*NS*
Clinical presentation			*NS*
Stable angina	*21 (36%)*	*8 (20%)*	
Unstable angina	*20 (34%)*	*18 (44%)*	
Non-ST elevation myocardial infarction	*12 (20%)*	*7 (17%)*	
ST elevation myocardial infarction	*6 (10%)*	*8 (20%)*	
Fibrinogen (mg/dl)	*254±45*	*289±49*	*0.003*
LDL-cholesterol (mg/dl)	*128±63*	*136±38*	*NS*
Lipoprotein (a) (mg/dl)	*31±25*	*31±27*	*NS*
Monocyte (/mm^3)	*421±158*	*646±212*	*<0.001*
Ejection fraction (%)	*64.6±8.9*	*59.7±10.4*	*0.014*
Statin therapy	*35 (59%)*	*25 (61%)*	*NS*
6-month follow-up LDL-cholesterol (mg/dl)			
Statin use	*95±28*	*102±45*	*NS*
No statin use	*127±61*	*130±32*	*NS*

CAD, coronary artery disease; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein.

Methods

Study Population

Our patient population comprised 100 consecutive patients (100 lesions) who underwent successful IVUS-guided stent implantation. The patients were scheduled to undergo elective stent implantation for de novo lesions in native coronary arteries having a diameter between 2.5 and 4.0 mm. The patients with acute ST elevation myocardial infarction within 24 h before admission, left main disease, bifurcation lesions, graft stenosis, and left ventricular dysfunction (left ventricular ejection fraction <40%) were excluded. Among these patients, 60 received statin treatment: simvastatin, pravastatin, and atorvastatin.

Laboratory Analysis

In all patients, serum was collected immediately before the initial PCI for measurement of hs-CRP level by immunoturbidimetric CRP-Latex (II) hs assay using an Olympus 5431 autoanalyzer. The assay was performed according to the manufacturer's protocol and has been validated against the Dade-Behring method[11] The assay has a coefficient of variation of ≈5%. Levels >0.5 mg/dl were considered elevated.

Stent Implantation Procedure

Stent implantation was performed as previously described[12] using bare metallic MAC stents. All patients received aspirin (300 mg at least 12 h prior to stent implantation and 100–200 mg daily, indefinitely) and ticlopidine (500 mg at least 6 h prior to stent implantation and 250 mg daily continued for 30 days) or clopidogrel (300 mg at least 6 h prior to stent implantation and 75 mg daily continued for 30 days). A coronary angiogram was performed using the femoral or radial arteries. Dalteparin was administered 120 U/kg of body weight intravenously every 12 h or unfractionated heparin as an intravenous bolus (usually 5,000 units) followed by a continuous infusion at a dose adjusted according to the activated partial thromboplastin time. All stenotic lesions were pre-dilated and stents were deployed at 10–18 atm. Each angiogram or IVUS sequence was preceded by 200–300 μg of intracoronary nitroglycerin.

Quantitative Coronary Angiography (QCA)

The angiograms were analyzed by a validated QCA system (Phillips H5000 or Allura DCI program). Minimal luminal diameter, reference diameter and percent diameter stenosis were measured in identical views before percutaneous balloon angioplasty and immediately after stent implantation.

Analysis of IVUS Images

We used the Endosonics IVUS system, which allows digital storage of pullback sequences. Automated pullbacks at 1 mm/s were performed before intervention and repeated after stenting. The IVUS measurements were performed at the tightest segment within the stent and at the proximal and distal references. Trained catheterization laboratory personnel performed the IVUS measurements according to previously described methods[13] Pre-interventional lesion external elastic membrane (EEM), lumen, and plaque and media (P&M = EEM − lumen) cross-sectional areas (CSA) were measured and plaque burden was calculated by lesion P&M/lesion EEM. The lesion was the site with the smallest lumen CSA; if there were multiple image slices with the same minimum lumen CSA, then the slice with the largest EEM and P&M was measured. Pre-interventional arterial remodeling was assessed by comparing the lesion site EEM to the proximal and distal reference EEM CSA: positive remodeling (PR, lesion >proximal reference), intermediate remodeling (distal reference< lesion< proximal reference), and negative remodeling (lesion< distal reference). The remodeling index (RI) was defined as: target lesion EEM CSA divided by the average of the proximal and distal reference EEM CSA. Post interventional and follow-up stent, lumen, and NIH (stent minus lumen CSA) areas were measured.

Restenosis of the Target Lesion

The patients were observed for the incidence of resteno-

Table 2 Baseline Angiographic and Procedural Characteristics

	Normal CRP (n=59)	Elevated CRP (n=41)	p value
Target artery			NS
Left anterior descending artery	45 (76%)	28 (68%)	
Left circumflex artery	10 (17%)	6 (15%)	
Right coronary artery	4 (7%)	7 (17%)	
Lesion morphology			0.001
B_1	59 (100%)	34 (83%)	
B_2	0 (0%)	7 (17%)	
No. of diseased vessels			NS
1	54 (92%)	35 (85%)	
2	5 (9%)	6 (15%)	
Lesion length (mm)	14.18±3.21	15.11±3.45	NS
Stent size (mm)	3.31±0.33	3.42±0.38	NS
Stent length (mm)	17.12±3.10	17.92±3.21	NS
Reference vessel size	3.10±0.80	3.29±0.70	NS
Minimal lumen diameter (mm)			
Pre-intervention	1.04±0.55	1.00±0.59	NS
Post-intervention	2.78±0.56	2.91±0.43	NS
Follow-up	2.24±0.64	1.96±0.65	0.013
Late loss	0.54±0.34	0.95±0.42	0.011
Diameter stenosis (%)			
Pre-intervention	66±17	70±15	NS
Post-intervention	10±6	12±7	NS
Follow-up	28±10	40±15	0.009

CRP, C-reactive protein.

Table 3 Quantitative Intravascular Ultrasound Results

	Normal CRP (n=59)	Elevated CRP (n=41)	p value
Pre-intervention			
Proximal reference EEM CSA (mm^2)	16.3±3.3	16.7±2.8	NS
Lesion segment EEM CSA (mm^2)	12.2±3.4	15.8±3.3	<0.001
Lesion segment lumen CSA (mm^2)	3.9±0.7	4.3±1.0	NS
Lesion segment P&M CSA (mm^2)	8.3±3.2	11.5±3.1	<0.001
Lesion segment plaque burden (%)	66.2±7.7	72.1±6.6	0.032
Distal reference EEM CSA (mm^2)	12.0±3.5	12.5±2.7	NS
Remodeling pattern			NS
Positive remodeling	8 (14)	13 (32)	
Intermediate remodeling	28 (48)	16 (39)	
Negative remodeling	23 (39)	12 (29)	
Remodeling index	0.93±0.13	1.02±0.11	<0.001
Post-intervention stent CSA (mm^2)	7.4±1.7	7.6±1.8	NS
Follow-up			
Proximal reference EEM CSA (mm^2)	16.2±3.4	16.6±2.3	NS
Lesion segment EEM CSA (mm^2)	12.4±3.5	15.4±3.1	<0.001
Stent CSA (mm^2)	7.3±1.6	7.5±1.7	NS
Intra-stent lumen area (mm^2)	5.2±1.1	4.5±1.7	0.011
Intra-stent NIH area (mm^2)	1.9±1.3	3.0±1.5	0.001
Distal reference EEM CSA (mm^2)	11.9±3.2	12.4±2.3	NS
Net decrease of lumen CSA (mm^2)	–2.2±1.6	–3.1±0.8	0.001
Net increase of NIH area (mm^2)	1.9±1.3	3.0±1.5	0.001

CRP, C-reactive protein; EEM, external elastic membrane; CSA, cross-sectional area; P&M, plaque plus media; NIH, neointimal hyperplasia.

sis and repeat PCI during the follow-up period. Angiography was repeated at 6 months after PCI and angiographic restenosis was defined as stenosis more than 50% of target lesion on follow-up. Clinical follow-up was successfully performed for all patients.

Statistical Analysis

Statistical analysis was performed using commercially available software (SPSS Version 11, Chicago, IL, USA). For the statistical analyses, the unpaired t-test and chi-square test were performed and the results were designated as the mean value ± SD or number (%) of patients. A p-value of less than 0.05 was considered significant.

Results

Baseline Characteristics

The patients' baseline clinical characteristics are summarized in Table 1. The baseline CRP level was 0.29± 0.08 mg/dl in the normal CRP group and 2.90±2.31 mg/dl in the elevated CRP group. The levels of fibrinogen and monocytes were higher and the ejection fraction was lower

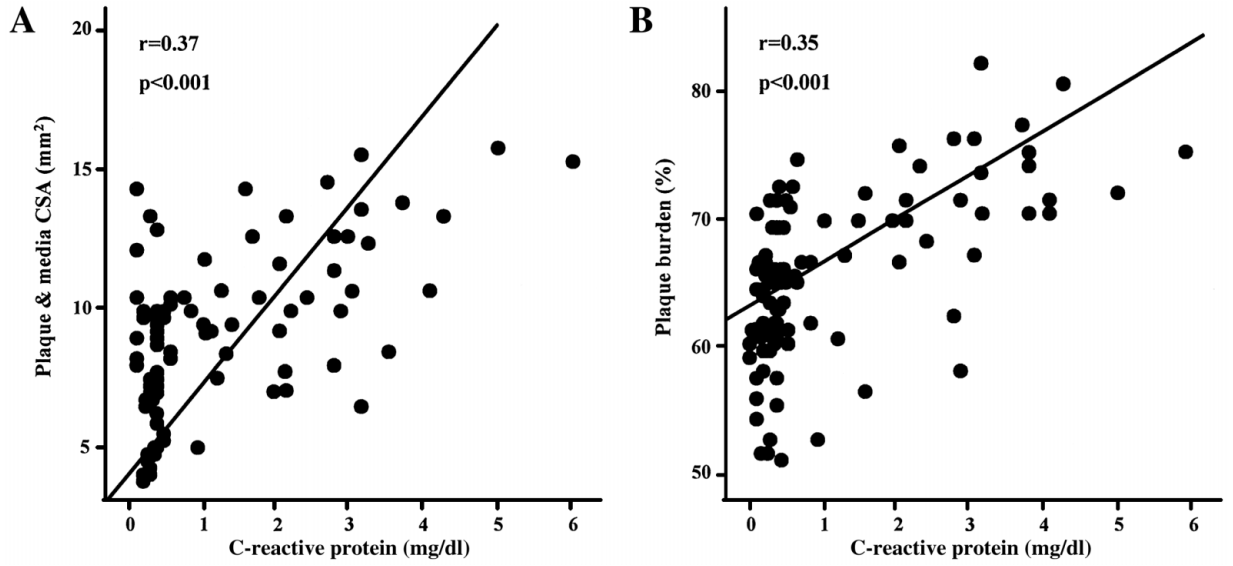

Fig 1. Correlation between pre-interventional C-reactive protein level and pre-interventional plaque plus media cross-sectional area (CSA) (A) and pre-interventional plaque burden (B).

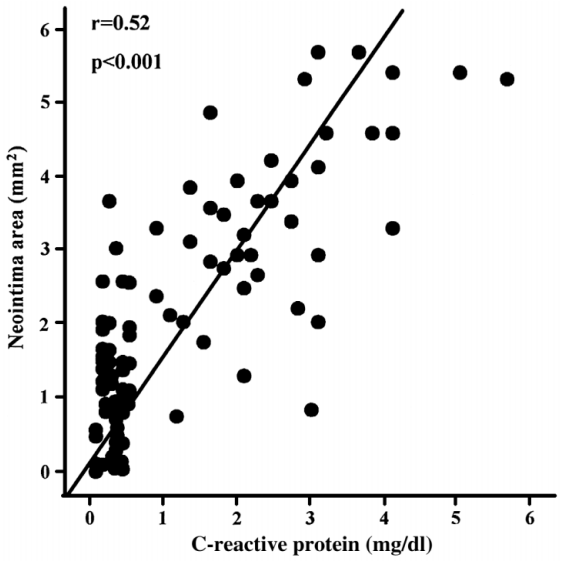

Fig 2. Correlation between pre-interventional C-reactive protein level and follow-up neointimal hyperplasia area.

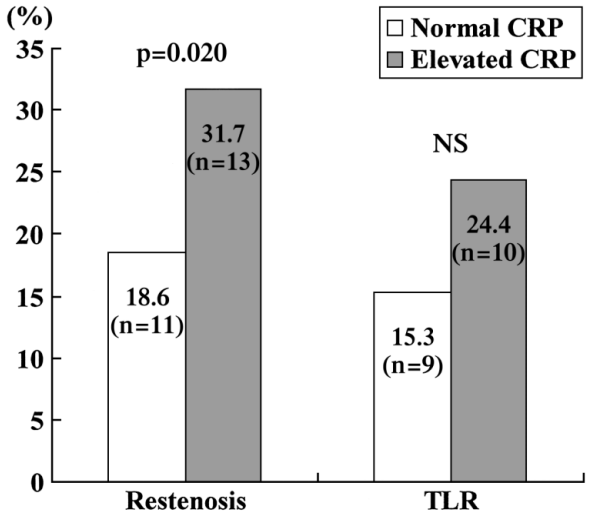

Fig 3. Incidences of restenosis and target lesion revascularization (TLR) according to the pre-interventional C-reactive protein (CRP) level. The number of patients in the normal CRP and elevated CRP groups was 59 and 41.

in the elevated CRP group.

Angiographic and QCA Results

Angiographic results are summarized in Table 2. On the diagnostic coronary angiograms, complex lesions were observed more frequently in the elevated CRP group. On the follow-up angiograms, the late loss was significantly larger in the elevated CRP group compared with the normal CRP group (0.54±0.34 mm vs 0.95±0.42 mm, p=0.013).

IVUS Results

IVUS results are summarized in Table 3. The pre-interventional EEM CSA at lesion segment (12.2±3.4 mm^2 vs 15.8±3.3 mm^2, p<0.001) was significantly larger in the elevated CRP group, as was the pre-interventional lesion P&M CSA (8.3±3.2 mm^2 vs 11.5±3.1 mm^2, p<0.001), and the plaque burden was significantly greater (66.2±7.7% vs 72.1±6.6%, p=0.032). The RI was 0.93±0.13 in the normal CRP group and 1.02±0.11 in the elevated CRP group (p<0.001). A significant positive correlation was found between pre-interventional CRP level and pre-interventional P&M CSA and plaque burden (r=0.37, 0.35, p< 0.001, <0.001, respectively) (Fig 1). At 6-month follow-up, intra-stent lumen area was significantly smaller in the elevated CRP group (5.2±1.1 mm^2 vs 4.5±1.7 mm^2, p=0.011) and NIH area was significantly larger (1.9±1.3 mm^2 vs 3.0± 1.5 mm^2, p=0.001). The net decrease of lumen CSA was significantly greater in the elevated CRP group (2.2± 1.6 mm^2 vs 3.1±0.8 mm^2, p=0.001) and the net increase of NIH area was significantly greater (1.9±1.3 mm^2 vs 3.0± 1.5 mm^2, p=0.001) (Table 3). A significant positive correlation was found between pre-interventional CRP level and

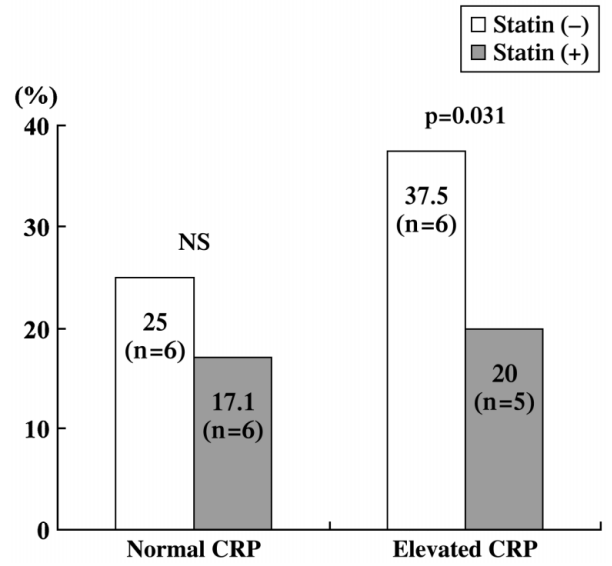

Fig 4. Incidence of restenosis according to the pre-interventional C-reactive protein (CRP) level and the use of statins. The number of patients in the non-statin and statin groups was 24 and 35 in the normal CRP group and 16 and 25, respectively, in the elevated CRP group.

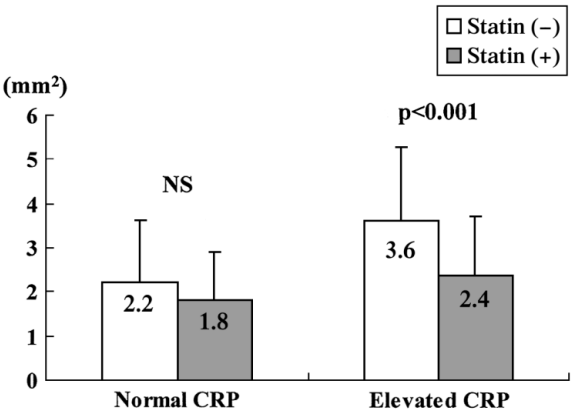

Fig 5. Intra-stent neointimal area at 6-month follow-up according to the pre-interventional C-reactive protein (CRP) level and the use of statins. The number of patients in the non-statin and statin groups was 24 and 35 in the normal CRP group and 16 and 25, respectively, in the elevated CRP group.

follow-up NIH area (r=0.52, p<0.001) (Fig 2).

Restenosis and Revascularization According to the Preprocedural CRP Level

When the categorical criterion of ≥50% diameter stenosis at follow-up was used to assess restenosis development, the restenosis rate was 18.6% in the normal CRP group and 31.7% in the elevated CRP group (p=0.020). The revascularization rate was 15.3% in the normal CRP group and 24.4% in the elevated CRP group. However, this was not statistically significant (Fig 3).

Restensosis Rate and Neointima Area According to the Preprocedural CRP Level and the Use of Statins at 6-Month Follow-up

We analyzed the restenosis rate according to the preprocedural CRP level and the use of statins. In patients with normal CRP, there was no association between the use of statins and the incidence of restenosis (17.1% vs 25%). However, when the analysis was confined to patients with elevated CRP, statin therapy significantly reduced the restenosis rate (20% vs 37.5%, p=0.031) (Fig 4). In the normal CRP group, the intra-stent neointimal area at 6 months was not different between the non-statin and statin groups (2.2±1.4 mm^2 vs 1.8±1.1 mm^2). However, in the elevated CRP group, statin therapy significantly decreased the neointimal area at 6-month follow-up (3.6±1.7 mm^2 vs 2.4±1.3 mm^2, p<0.001) (Fig 5).

Discussion

Despite the importance of CRP level in the management of CAD, very few clinical studies have addressed the relationship between its pre-procedural level and NIH. The results of this study demonstrate that an elevated pre-procedural CRP level is associated with large pre-interventional P&M CSA and follow-up NIH area on serial follow-up IVUS and is associated with a higher incidence of restenosis in patients who were not treated with statins after coronary stent implantation.

Stent implantation for CAD is now established as a therapeutic strategy with great benefit![14,15] However, in-stent resenosis, which is the main limitation, remains unresolved. Recently, it has been shown that many drug-eluting stents effectively inhibit NIH after stent implantation![16,17] In our previous study,[18] we reported that abciximab-coated stent effectively inhibited NIH on serial follow-up IVUS after stent implantation, so vasculoprotective agents such as abciximab may provide an alternative approach to antiproliferative agents in the prevention of in-stent restenosis.

Excessive in-stent NIH is the main contributing factor to in-stent restenosis![19,20] Experimental and clinical studies have suggested that inflammation plays an important role in the pathogenesis of intimal hyperplasia after arterial injury.[21,22] Other animal studies have demonstrated that after stenting, a particularly brisk early inflammatory response is induced with abundant surface adherent monocytes and granulocytes.[23] Several days and weeks later, macrophages invade the forming neointima and are observed clustering around stent struts.[23] Systemic inflammatory reaction may play a pivotal role in neointimal formation within stent struts in addition to the local vessel wall injury with the subsequent release of chemotactic and growth factors.[24,25]

Several clinical studies have shown that the pre-procedural CRP level is a strong prognostic factor of mortality and subsequent cardiac events including clinical restenosis.[26] Buffon et al reported that the baseline CRP was the most powerful predictor of clinical restenosis after balloon angioplasty.[27] Zairis et al reported that the incidence of death, or myocardial infarction, during a 2-year follow-up, after elective coronary angioplasty, was 3.9-fold higher in patients with increased baseline CRP levels.[28] Kawamoto et al[29] compared the impact of inflammatory response on restenosis after coronary stenting and directional coronary atherectomy and demonstrated that the levels of CRP and macrophages were greater in patients with in-stent restenosis than in those with restenosis after directional coronary atherectomy. Therefore, they suggested that the inflammatory response is more involved in the pathogenesis of in-stent restenosis than in restenosis after directional coronary atherectomy. Angioi et al reported that patients with reste-

nosis had significantly higher levels of CRP than those without restenosis (0.68 mg/dl vs 0.21 mg/dl, p<0.001) and when the patient population was divided by tertiles of CRP, the incidence of restenosis significantly increased from the first to the third tertiles (restenosis rate: 17% vs 42% vs 72%, p<0.003).[30] In our previous study performed in patients with acute myocardial infarction, we reported that the incidence of cardiogenic shock was higher in the elevated CRP group than in the normal CRP group (3/86, 3.5% vs 15/122, 12.3%, p=0.026) and the 1-year survival rate was significantly lower in the elevated CRP group than in the normal CRP group (96.5% vs 86.9%, p=0.018).[31]

In the present study, the pre-interventional lesion P&M CSA was significantly larger in the elevated CRP group and the plaque burden was significantly greater, and a significant positive correlation was found between pre-interventional CRP levels and pre-interventional P&M CSA and plaque burden. At 6-month follow-up, intra-stent lumen area was significantly smaller in the elevated CRP group and NIH area was significantly larger, and a significant positive correlation was found between pre-interventional CRP levels and follow-up NIH CSA. These results indicate that pre-procedural CRP may predict in-stent restenosis, supporting the role of inflammation in intimal hyperplasia. Our results may assist in stratifying lesions at high-risk for in-stent restenosis in patients undergoing stent implantation.

Patterns of arterial remodeling during the course of plaque development have been shown to play an important role in both the progression of de novo atherosclerosis[32] and the restenotic process following PCI.[33] Okimoto et al reported that atherosclerotic plaque morphology, as defined by quantitative analysis of IVUS images, was related to the immunohistochemical findings.[34] In the present study, the RI was significantly higher in the elevated CRP group, which indicates that a highly inflammatory state as expressed by elevated CRP is associated with vascular remodeling and NIH.

Statins inhibit mevalonate synthesis and effectively lower the level of LDL-C. Beyond lowering lipids, statins have favorable effects on vascular inflammation,[35,36] endothelial function,[37] platelet adhesion and thrombosis.[38] The anti-atherothrombotic effects of statins clearly have potential for benefiting patients with CAD. Statins promote atherosclerotic plaque stabilization via inhibition of inflammatory macrophages, depletion of the lipid core, and strengthening of the fibrous cap. Statins are now recognized as anti-inflammatory agents that downregulate inflammatory cytokines and C-reactive protein.[39–41] Few data are available for the effects of statins on restenosis and target lesion revascularization after PCI. Mulder et al reported that pravastatin significantly reduced the restenosis rate in the treatment group compared with the placebo group at 2-year follow-up (7% vs 29%).[2] Walter et al reported that the 6-month restenosis rate was significantly lower in the statin-treated group than in the placebo group (25.4% vs 38%).[43] In the present study, at 6-month follow-up the restenosis rate was 18.6% in the normal CRP group and 31.7% in the elevated CRP group. There was no association between the use of statins and the incidence of restenosis in the normal CRP group, but when the analysis was confined to patients with elevated CRP, statin therapy significantly reduced the restenosis rate and decreased NIH compared with patients in the normal CRP group. These findings strongly suggest that the anti-restenotic and anti-proliferative effects of statins in patients with elevated CRP are associated with favorable effects on vascular inflammation, endothelial function, platelet adhesion and thrombosis beyond lowering of the lipid levels.

Study Limitations

First, the group sizes are relatively small. Second, we used the Endosonics IVUS system with a pullback speed of 1 mm/s, but the accuracy of these measurements has not been established. The pullback speed is too fast for precise measurement. Moreover, the longitudinal measurement of Endosonics IVUS pullback is not accurate. Third, because pre-interventional IVUS imaging was performed according to the operator's decision, lesion selection may be biased. Fourth, serial follow-up of the serum hs-CRP level was not done, so we did not demonstrate the impact of sequential change in the hs-CRP level on NIH after stent implantation.

Conclusion

Our study shows that the serum level of hs-CRP before stent implantation is related to both pre-interventional plaque growth and NIH after successful stent implantation, and that statin therapy may reduce the restenosis rate in patients with elevated hs-CRP. Therefore, the measurement of the pre-procedural hs-CRP level could provide the basis for risk stratification before stent implantation for CAD and may be a useful tool in targeting aggressive anti-inflammatory therapy to patients who have the highest risk for ischemic complications or restenosis after coronary stent implantation. Intensive statin therapy should be recommended for patients with CAD who have elevated CRP levels.

Acknowledgment

This study was supported by the 2005 Research Fund of Cardiovascular Research Foundation Asia.

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