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 mm² vs 3.0±1.5 mm², 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 mm² vs 1.8±1.1 mm²). However, in the elevated CRP group, statin therapy significantly decreased the neointimal area at 6-month follow-up (3.6±1.7 mm² vs 2.4±1.3 mm², 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.

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Key Words: Inflammation; Restenosis; Stent
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 1478 autoanalyzer. The assay was performed according to the manufacturer’s protocol and has been validated against the Dade-Behring method. 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 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 mg 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. 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 (stenus minus lumen CSA) areas were measured.

Restenosis of the Target Lesion

The patients were observed for the incidence of resteno-
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 as the mean value±SD or number (%) of patients. A p-value of less than 0.05 was considered significant.
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 mm² vs 15.8±3.3 mm², p<0.001) was significantly larger in the elevated CRP group, as was the pre-interventional lesion P&M CSA (8.3±3.2 mm² vs 11.5±3.1 mm², 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 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.
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).

Restenosis 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 pre-procedural 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 mm² vs 1.8±1.1 mm²). However, in the elevated CRP group, statin therapy significantly decreased the neointimal area at 6-month follow-up (3.6±1.7 mm² vs 2.4±1.3 mm², 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. However, in-stent restenosis, which is the main limitation, remains unresolved. Recently, it has been shown that many drug-eluting stents effectively inhibit NIH after stent implantation. In our previous study 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 anti-proliferative agents in the prevention of in-stent restenosis.

Excessive in-stent NIH is the main contributing factor to in-stent restenosis. Experimental and clinical studies have suggested that inflammation plays an important role in the pathogenesis of intimal hyperplasia after arterial injury. Other animal studies have demonstrated that after stenting, a particularly brisk early inflammatory response is induced with abundant surface adherent monocytes and granulocytes. Several days and weeks later, macrophages invade the forming neointima and are observed clustering around stent struts. 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.

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. Buffon et al reported that the baseline CRP was the most powerful predictor of clinical restenosis after balloon angioplasty. 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. Kawamoto et al 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.
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

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References


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