ance of High-Sensitivity C-Reactive Protein ngioplasty in Patients With Stable Angina Pectoris

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Abstract:

We examined whether an increase in high-sensitivity C-reactive protein (hs-CRP) after percutaneous coronary intervention (PCI) predicts long-term prognosis in patients with stable angina pectoris. hs-CRP is an inflammatory marker that predicts future cardiovascular events in healthy subjects and patients with unstable and stable coronary syndromes. Long-term evaluation of pre- and postprocedural inflammatory markers has not been widely reported. In particular, the effect of the magnitude of increase in hs-CRP after PCI in stable patients is unknown. We prospectively analyzed 89 stable patients treated by PCI for stable angina pectoris. Patients were recruited between August 1998 and May 1999, and the population was followed until August 2005 (mean follow-up 79.5 ± 10.3 months). A major adverse cardiac event (MACE) was defined as the occurrence of cardiac death, myocardial infarction, or recurrent angina requiring repeat PCI or coronary artery bypass grafting. During the follow-up period, 36 patients presented with Ó1 MACE. In multivariate analysis, independent predictors of the occurrence of MACEs were previous myocardial infarction and a significant increase in hs-CRP after PCI ($p = 0.004$ and 0.003, respectively). A significant increase in hs-CRP after PCI was found to be more predictive of MACEs than hs-CRP before and after PCI. In conclusion, in stable coronary artery disease, inflammation is associated with long-term adverse events, but the magnitude of the inflammatory reaction after PCI appears more predictive than the baseline value.

A previous study[1] has reported that high-sensitivity C-reactive protein (hs-CRP) increases after percutaneous coronary intervention (PCI) in patients with unstable angina pectoris and high baseline hs-CRP levels, but not in those with normal baseline hs-CRP. An increase in hs-CRP levels after PCI in this unstable condition does not seem to be related to the treated plaque but may rather be a marker of the inflammatory state. In stable coronary artery disease, it is unknown whether the magnitude of increase in hs-CRP after PCI provides independent prognostic information. The purposes of this study were to analyze the long-term prognostic importance of pre- and postprocedural hs-CRP and of the magnitude of hs-CRP increase in patients treated by elective PCI for stable angina pectoris.

Methods and Results

Between August 1998 and May 1999, we prospectively analyzed 89 consecutive patients who were referred for coronary angiography for stable angina and exercise-induced ischemia. They underwent PCI of Ó1 coronary stenosis. Exclusion criteria were age Ó80 years, history of acute coronary syndrome with or without ST-segment elevation within the previous year, treatment for restenosis, coronary artery bypass grafting, or PCI within the previous 6 months, heart failure of New York Heart Association class Ó3, or known malignant or inflammatory disorders. Six-year follow-up was obtained in all patients by inspection of medical records. To ensure that no deaths were missed, the general practitioner was contacted to provide clinical evolution and treatment regimens, and if the patient had died, to specify cause of death. Major adverse cardiac events (MACEs) were defined as the occurrence of cardiac death, myocardial infarction, unstable angina, and any coronary revascularization (surgery and/or PCI). Myocardial infarction was defined as the occurrence of typical chest pain associated with an increase in creatine kinase-MB Ó3 three times above the upper normal limit or with the development of new pathologic Q waves on electrocardiography. The study was approved by the local ethics committee, and all patients gave informed consent.

n each patient on the day before and 24 hours after PCI. Multiple in Table 1. hs-CRP assays were measured by rate nephelometry atex C-reactive protein mono Analyzer, Behring Diagnostic, Marburg, Germany). The lower detection limit was 0.175 mg/L. Because in epidemiologic studies differences of 3 mg/L distinguish patients of low, intermediate, and high risk,[2-5] an increment in hs-CRP after PCI (ΔhsCRP) ≥3 mg/L was considered significant.

Selective coronary angiography was performed through the femoral route using a 6Fr introducer sheath. Serial coronary angiograms of the left and right coronary arteries were obtained after intracoronary administration of isosor-bide dinitrate (0.2 to 0.4 mg). After diagnostic evaluation, PCI with or without stenting was performed. Heparin (70 U/kg) was given before introduction of the guidewire. No patient received glycoprotein IIb/IIIa inhibitors, but all were pretreated with ticlopidine (500 mg) ≥4 hours before intervention. All patients were treated with aspirin indefinitely, and 250 mg of ticlopidine 2 times daily was added for 4 weeks in patients treated by stenting.

***Table 1**: Characteristics of the population*

Variable	Before PCI (n = 89)	After PCI (n = 89)	æ (after ð before) (n = 89)
Age (yrs)	60.2 ± 10.2		Not applicable
Body mass index (kg/m^2)	27.6 ± 3.4		Not applicable
Men	67 (75.3%)		Not applicable
Current smoker	48 (53.9%)		Not applicable
Diabetes mellitus	16 (18%)		Not applicable
Hypertension	48 (53.9%)		Not applicable
Previous myocardial infarction	23 (25.8%)		Not applicable
Previous coronary artery bypass grafting	8 (9%)		Not applicable
Previous PCI	24 (27%)		Not applicable
Statin treatment	16 (18%)	80 (90%)	64
Ejection fraction <50%	10 (11.2%)		Not applicable
Stent	57 (64%)		Not applicable
Folic acid (ng/ml)	6 ± 2.35		Not available
Homocysteine (µmol/L)	11 ± 4.2		Not available
Fibrinogen (g/L)	2.88 ± 0.7	3.17 ± 0.6	0.29
Total creatine kinase (UI/L)	91.7 ± 46.3	135.39 ± 113.8	43.69
Creatine kinase-MB (µg/L)	2.01 ± 1.2	6.74 ± 9.4	4.73
Myoglobin (µg/L)	20.38 ± 14.3	38.17 ± 57.1	17.79
Troponin T (µg/L)	0.01	0.11 ± 0.3	0.1
hs-CRP (mg/L)	3.35 ± 5.1	8.69 ± 8.8	5.34
Triglycerides (mg/dl)	217 ± 160	226 ± 150	9
Total cholesterol (mg/dl)	218 ± 40	209 ± 40	-9
LDL cholesterol (mg/dl)	134 ± 30	127 ± 40	-7
Apolipoprotein Al (mg/dl)	121 ± 20	133 ± 20	12
Apolipoprotein B (mg/dl)	104 ± 20	106 ± 20	2
Lipoprotein (a) (mg/dl)	23 ±30	25 ±30	2
Oromucosoid (g/L)	0.74 ± 0.2	0.92 ± 0.2	0.18

Values expressed as means ± SDs for age and body mass index and as means ± SEMs for other values. LDL = low-density lipoprotein.

Continuous variables are expressed as mean ± 1 SD. Differences between mean values were assessed by Student's *t* test (for normally distributed variables) and by the nonparametric Kruskal-Wallis test for other variables. Categorical variables were compared with chi-square test. The Kaplan-Meier method was used for cumulative MACE-free survival analysis. The effect of covariates on survival times was tested by Cox proportional hazards regression analysis. Correlation between quantitative variables was assessed by means of Spearman's correlation coefficient. Cut-off points of differences between CRP values before and after intervention were derived by the likelihood ratio procedure. Results were considered significant at the 5% critical

l with SAS 9.1 for Windows (SAS Institute, Cary, North on, Seattle, Washington).

Clinical, biological, and angiographic characteristics of the studied population are listed in Table 1. Angiographic procedural success was obtained in all patients, with no in-hospital complications.

Median hs-CRP levels were 3.35 mg/L before intervention and 8.69 mg/L after PCI. Most patients presented with at least a slight increase in this parameter (mean qhs-CRP 5.34 mg/L). A significant qhs-CRP after PCI (Ó3 mg/L) was observed in 43 patients.

To evaluate whether intense inflammatory reaction was linked to embolization and minor myocardial damage, we compared changes in hs-CRP and troponin T. There was no correlation between a qhs-CRP level >3 mg/L and a qtro-ponin T level >0.0l µg/L (Figure 1).

Patients showing a qhs-CRP level >3 mg/L after PCI had a higher incidence of previous myocardial infarction and a lower ejection fraction. Mean fibrinogen values before and after PCI were also higher in these patients, who otherwise did not differ from patients without a significant increase in hs-CRP after PCI (Table 2).

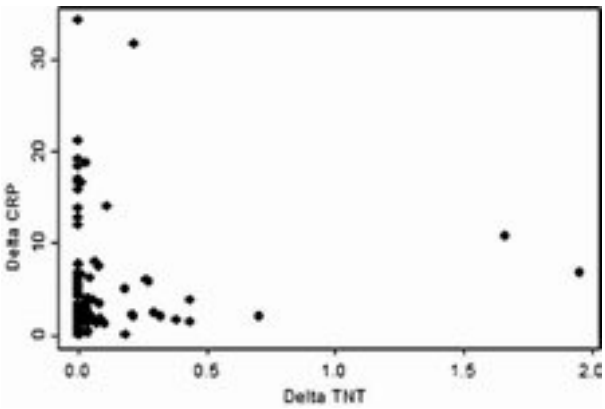
During follow-up, 36 patients presented with 1 MACE: 1 patient died of cardiac cause (sudden death); 6 patients presented with acute myocardial infarction (2 with Q wave and 4 with non-Q wave); 6 patients underwent coronary bypass grafting for recurrent ischemia; 12 patients were treated by PCI on a lesion other than the initial lesion; and 11 patients presented with symptomatic restenosis that was treated by repeat PCI. Of these, 33 events occurred in patients with a significant qhs-CRP level, and only 3 events happened in patients with a qhs-CRP level <3 mg/L.

Figure 2 presents Kaplan-Meier event-free survival curves in patients with or without a significant increase in hs-CRP after PCI. The higher rate of events in patients with a qhs-CRP level >3 mg/L was observed throughout the follow-up period at 1 year (18% vs 2.2%, p <0.000l) and after 6.6 years (37% vs 3.4%, p <0.000l).

Univariate predictors of MACEs were previous myocardial infarction, left ventricular ejection fraction <50%, ab-normal values after PCI in myoglobin and hs-CRP, and a qhs-CRP level >3 mg/L. In multivariate analysis, previous myocardial infarction and a qhs-CRP level >3 mg/L were independent predictors of long term-outcome (p = 0.004 and 0.003, respectively; Table 3).

An increase in hs-CRP level >3 mg/L after PCI had a higher predictive value for the occurrence of MACEs than hs-CRP before and after PCI considered separately. The Kaplan-Meier event-free survival curve according to hs-CRP and troponin T variations is presented in Figure 3.

Figure 1. *Correlation between a **q**hs-CRP level >3 mg/L and a **q**troponin T level >0.0l µg/L (r = -0.023, p = NS).*



ccording to level of change in high-sensitivity C-reactive protein

	Change in CRP After Intervention		p Value
	<3 mg/L (n = 46)	Ó3 mg/L (n = 43)	
Age (yrs)	59.9 ± 9.4	60.5 ± 11.1	0.80
Men	38 (83%)	29 (67%)	0.097
Smoker	25 (54%)	23 (53%)	0.94
Diabetes mellitus	8 (17%)	8 (19%)	0.88
Hypertension	25 (54%)	23 (53%)	0.94
Previous myocardial infarction	7 (15%)	16 (37%)	0.018*
Previous coronary artery bypass grafting	2 (4%)	6 (14%)	0.11
Previous PCI	12 (26%)	12 (28%)	0.85
Statins	9 (20%)	7 (16%)	0.69
Ejection fraction Ò50%	2 (4%)	8 (19%)	0.033*
Stent	30 (65%)	27 (63%)	0.81
Height (cm)	170 ± 7.8	169 ± 9.2	0.71
Weight (kg)	80 ± 11	79 ± 12	0.63
Before PCI			
Fibrinogen (g/L)	2.7 ± 0.60	3.1 ± 0.76	0.032*
Creatine kinase (UI/L)	94 ± 48	89 ±44	0.65
Creatine kinase-MB (µg/L)	2.0 ± 1.1	2.1 ± 1.2	0.58
Myoglobin (µg/L)	20.2 ± 11.5	20.5 ± 17.0	0.92
Troponin T >0.01 µg/L	2 (4%)	1 (2%)	0.60
Lipoprotein (a) (mg/dl)	24 ±26	23 ±27	0.94
After PCI			
Fibrinogen (g/L)	3.0 ± 0.67	3.4 ± 0.48	0.0077*
Creatine kinase (UI/L)	124 ± 94.6	148 ± 131	0.34
Creatine kinase-MB (µg/L)	5.5 ± 6.3	8.0 ± 12	0.22
Myoglobin (µg/L)	26.5 ± 16.2	50.6 ± 79.1	0.056
Troponin T (µg/L)	0.08 ± 0.14	0.14 ± 0.39	0.36
Change in troponin T	0.07 ± 0.14	0.13 ± 0.39	0.36
Lipoprotein (a) (mg/dl)	26 ± 29	25 ± 30	0.89

* p <0.05.

Discussion

The main findings of this study follow. In patients with stable angina pectoris who underwent PCI, the incidence of MACEs is higher in those with a significant increase in hs-CRP (>3 mg/L) after PCI in short- and long-term follow-up (18% vs 2.2% at 1 year and 37% vs 3.4% at a mean of 6.6 years, respectively). The 2 independent predictors of complications are a hs-CRP increase after PCI and previous myocardial infarction. A hsCRP increase induced by PCI yields a higher predictive value for MACEs than hs-CRP before or after PCI considered separately.

In stable patients, PCI triggers an inflammatory response that is not observed in patients undergoing coronary angiography without PCI.[6]

Increased CRP in this setting is not related to minor myocardial necrosis because we found no correlation between significant increases in hs-CRP and troponin T concentrations after PCI. A previous study found that patients with high inflammatory parameters at baseline were more likely to develop increased troponin, indicative of myocardial cell damage.[7] Thus, patients presenting with a high level of inflammatory markers before PCI appear to be more prone to develop microembolizations. This could explain the prognostic importance of CRP at baseline, at least for short- and mid-term outcomes.

Several reports have indicated that hs-CRP provides additional and independent prognostic information to the clinical and angiographic characteristics in patients undergoing PCI. In a large series of 727 patients treated by

tein IIb/IIIa inhibitor infusion, hs-CRP predicted 30-day
reated by elective angioplasty for stable coronary artery disease
ors were less frequently used, a hs-CRP level >3 mg/L was also a strong predictor of 2-year adverse coronary events.[9] In a cohort of 1,152 patients with stable angina treated by coronary stenting and followed for 1 year, Dibra et al[10] reported that a CRP level >5 mg/L was associated with an increased risk of death and myocardial infarction but had no effect on restenosis. Although these studies included large populations, they analyzed a relatively short-term outcome. Further, the use of different cut-off values of hs-CRP in these studies limits their application in clinical practice.

Figure 2. *Event-free survival curves of patients with and without a significant increase in hs-CRP after PCI.*

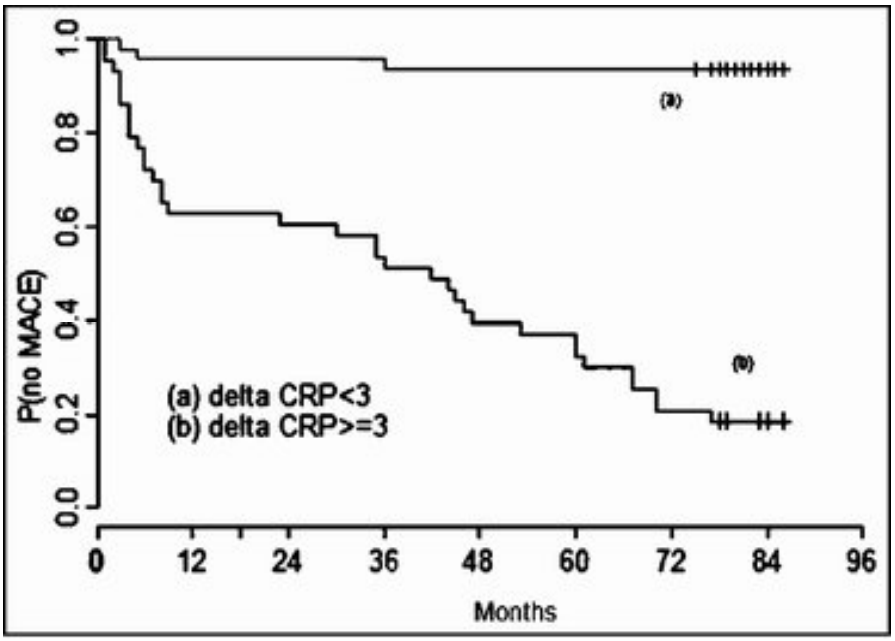


Table 3 *Predictors of major adverse cardiac events in univariate and multivariate analyses*

	Univariate Analysis		Multivariate Analysis	
	p Value	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)
Previous myocardial infarction	0.0002	3.5 (1.8-6.8)	0.004	2.80(1.4-5.64)
Left ventricular ejection fraction <50%	0.01	2.8 (1.2-6.5)	NS	
Myoglobin after PCI	0.05	1.004(1-1.008)	NS	
hs-CRP after PCI	0.0002	1.05 (1.02-1.07)	NS	
qhs-CRP	<0.0001	21.3 (6.5-70.3)	0.003	1.05 (1.02-1.09)

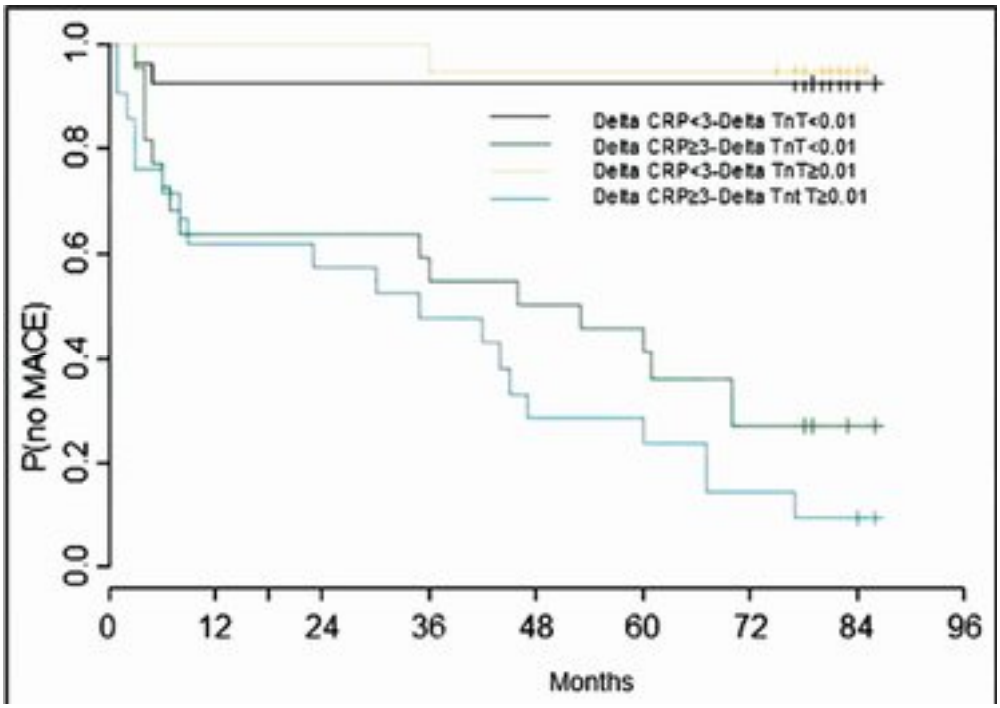
CI = confidence interval.

Late cardiac events usually result from the progression of atherosclerosis rather than from a complication of the PCI procedure (e.g., restenosis). Therefore, we think that it is crucial to extend the event horizon beyond 6 or 12 months to a longer period, as in the present study. Our study with a long-term follow-up confirms the strong prognostic effect of inflammation. This effect was not confined to the short term after PCI but was observed throughout the entire 6-year follow-up.

Although the level of inflammatory markers at baseline is clinically significant, the most powerful predictor of a worse outcome was the increase in such markers after PCI. A high hs-CRP level after PCI observed in some patients may reflect the hyper-responsiveness of their inflammation system to vascular aggression. Such hyper-reactivity ap pears to be a marker of increased progression of atherosclerosis and/or further clinical instability.

ug-elut-ing stents were used. All patients in this study were in a
sary applicable to other clinical settings.

Figure 3*. Event-free survival curves according to changes in hs-CRP and troponin T after PCI.*



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