C-Reactive Protein Plasma Levels but Not Factor VII Activity Predict Clinical Outcome in Patients Undergoing Elective Coronary Intervention

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Summary

Background: Both vascular inflammation as determined by C-reactive protein (CRP) and extrinsic coagulation as measured by factor VII activity (F VII) may predict clinical restenosis rate in patients with stable angina pectoris undergoing elective percutaneous coronary intervention (PCI).

Hypothesis: The primary objective of this study was to investigate the associations between baseline CRP levels, F VII activity, and restenosis rate after elective PCI in a 6-month follow-up period.

Methods: This prospective study included 81 patients aged ≥ 19 years undergoing PCI for angiographically significant ($\geq 70\%$) stenosis, with or without stenting, and 49 controls. Factor VII activity and CRP were measured in samples collected at angiography and 16–24 h post procedure after overnight fast. Successful PCI was defined as final diameter of $< 50\%$ with TIMI 3 flow and no complication within 1 h. After 6 months all patients who had undergone PCI were evaluated via a standardized questionnaire. Clinical restenosis was defined as the occurrence of a major adverse coronary events (MACE), within the follow-up period.

Results: Diagnostic angiography led to a significant increase in CRP levels after 16–20 h in patients with discrete CAD ($n = 22$) but not in patients without any signs of coronary atherosclerosis ($n = 27$). During a 6-month follow-up after PCI, 17 of 81 (21%) patients developed MACE. Tertiles of CRP levels independently predicted clinical restenosis, as it developed in 33.3% of patients with the highest CRP levels

(0.7–4.8 mg/dl), in 16.6% of patients with second tertile CRP levels (0.23–0.69 mg/dl), and in 7.4% of patients with lowest tertile CRP levels (0.0–0.22 mg/dl). There was a significant difference in the restenosis rate between patients from the first and the third tertiles ($p = 0.018$). Successful PCI was associated with a significant decrease of mean CRP levels after 6 months, whereas PCI in patients suffering from MACE led to no change in CRP levels. There was no association between factor VII activity and clinical outcome after PCI, and F VII activity did not change over a 6-month period.

Conclusions: In patients with stable angina pectoris undergoing elective PCI, increased preprocedural and 6-month follow-up CRP plasma levels are associated with clinical restenosis. Factor VII plasma activity lacks such correlations.

Key words: restenosis, stable angina, percutaneous coronary intervention, C-reactive protein, factor VII activity

Introduction

Although anatomical and biochemical risk factors for the development of restenosis after percutaneous coronary intervention (PCI) have been identified, an accurate preprocedural risk stratification is still lacking. Recent investigations suggest that the extent of the inflammatory response within the target lesion as well as coagulation factors play crucial roles in the development of restenosis.

Increased levels of inflammatory markers have been documented in various settings of coronary artery disease (CAD). Percutaneous coronary intervention as well is known to induce an inflammatory response within the vascular wall, and the magnitude of this response correlates with the degree of intimal hyperplasia. Both balloon angioplasty and stent implantation are accompanied by a short-term elevation of C-reactive protein (CRP) plasma levels.¹ C-reactive protein is a widely used nonspecific but sensitive marker of inflammation and/or acute phase responses. However, little data are available to show whether diagnostic coronary angiography without coronary intervention influences CRP levels. Long-term effects of PCI on systemic CRP levels are still unknown as well.

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Coagulation factor VII (F VII) is a key enzyme in the extrinsic coagulation pathway. It is activated by complex formation with tissue factor, while subsequent activation of factors IX and X initiates blood coagulation. Several clinical trials have demonstrated that a high level of F VII antigen is an independent risk factor for developing acute coronary syndromes.² Because of the key role F VII plays in the coagulation system, preinterventional high F VII activity could be a risk factor for clinical restenosis after PCI. Little is known about the influence of F VII activity in patients with stable angina undergoing elective PCI.

Therefore, the primary objective of this study was to investigate the associations between baseline CRP levels, F VII activity, and restenosis rate after elective PCI in a 6-month follow-up period.

Methods

Study Design and Patient Characteristics

The study was conducted as a prospective, single center, follow-up study. It was approved by the ethical committee of the University of Innsbruck. Patients eligible for the study were men and women aged ≥ 19 years undergoing elective angiography because of suspected stable CAD. Patients who underwent single- or multiple-vessel PCI with or without stenting for an angiographically significant ($\geq 70\%$) stenosis were included in the follow-up period. Exclusion criteria were as follows: pregnancy, liver disease, acute and chronic inflammatory condition known to be associated with elevated CRP or F VII activity, cancer, current thromboembolic event and myocardial infarction within 6 months, unstable angina, left ventricular function $< 30\%$ ejection fraction, anticoagulation therapy with heparin or coumarin prior to angiography, and chronic renal failure (serum creatinine ≥ 3 mg/dl). All subjects gave informed consent to participate in this study. The investigations were in accordance with the Declaration of Helsinki.

Percutaneous Coronary Intervention and Assessment of Restenosis

Angiographic results are expressed as the number of vessels (0–4) with stenosis of $\geq 70\%$ of the vessel diameter or occlusion of the vessel. Percutaneous coronary intervention was performed with balloon technique and was considered to be successful if the final percent diameter was $< 50\%$ with Thrombolysis in Myocardial Infarction (TIMI) 3 flow and no immediate complication within 1 h. The coronary angiograms were reviewed independently by experts who were blinded to the clinical outcomes. After 6 months, all patients who had undergone PCI were contacted and evaluated via a standardized questionnaire by an investigator blinded to clinical and biochemical data. Clinical restenosis was defined by the occurrence of a major adverse coronary event (MACE) such as angina pectoris with angiographically documented restenosis $> 50\%$, myocardial infarction, repeat PCI, coro-

nary artery bypass graft (CABG), and death with high probability of circulatory cause.

Measurement of Plasma Levels of C-Reactive Protein and Factor VII Activity

Blood samples were collected at the time of coronary angiography and 16–24 h after an overnight fast. Plasma was separated within 2 h. Highly sensitive CRP determination was performed from heparinized plasma samples with the fully automated Integra 700-system (lower detection limit 0.025 mg/dl) (Roche Diagnostics Corporation, Mannheim, Germany). Factor VII activity was measured in double determinations from citrate-containing plasma samples with the STA-coagulometer-analyzer (Roche Diagnostics Corporation). Values are expressed as a percentage of the value in pooled normal plasma. For the investigation of this study, calibration was performed from 11 to 180% using a commercially available pooled plasma (Standard Human Plasma, Dade Behring, Marburg, Germany).

Statistical Analysis

Regarding the normally distributed F VII activity levels, continuous variables are expressed as mean $\pm$ standard deviation (SD) and compared by *t*-test for paired and unpaired variables. The CRP levels did not follow normal distribution, and variables are expressed as median, range, and percentiles in box plots. Comparison between groups were carried out with the Mann-Whitney-U-test and pairwise comparison was performed with the Wilcoxon test. Categorical variables were compared by chi-square statistics or Fisher's exact test. Multiple logistic regression analysis was performed to establish the independent predictive value of preprocedural CRP in addition to other traditional prognostic risk factors (control of confounding). Traditional prognostic risk factors were considered to be the minimal lumen diameter post PCI, type of stenosis, and use of statins and thienopyridines. P-values of < 0.05 were considered statistically significant. All statistical tests were performed two-tailed and calculations were carried out with the Statistical Package for Social Sciences (SPSS Inc., Chicago, Ill., USA).

Results

In all, 81 patients undergoing elective PCI and 49 control patients were included in the study. Control groups included patients with angiographically normal coronary arteries ($n = 27$) as well as patients with angiographically detectable (stenosis $< 50\%$) but not significant CAD ($n = 22$). The baseline clinical, angiographic, and procedural characteristics of the study are summarized in Tables I and II. Except for the minimal lumen diameter after PCI, there was no significant difference in any clinical and procedural variable. After a mean follow-up of 6.8 ± 0.6 months, 17 of 81 patients (21%) had suffered from a major event: 8 patients needed repeat target vessel PCI (47%), 3 patients (18%) were submitted to CABG, 4 patients were kept on conservative therapy after angiographically doc-

TABLE I Baseline characteristics of the study population undergoing percutaneous coronary intervention according to major adverse coronary events (MACE) and no MACE during a 6-month follow-up

	No MACE n = 64	MACE n = 17
Age	62 ± 10	60 ± 10
Men (%)	46 (72)	10 (59)
Hypercholesterolemia (%) ^a	36 (56)	5 (29)
Smoking (%)	19 (30)	5 (30)
Hypertension (%) ^b	30 (47)	10 (59)
Diabetes mellitus (%)	8 (13)	4 (24)

^a Patients with abnormal serum cholesterol levels (> 200 mg/dl).^b Patients treated or with abnormal value.

umented restenosis (24%), and 2 patients suffered cardiac death (11%).

At discharge, 75% of patients were given adenosin receptor blocker clopidogrel, 68% statins, 57% beta-receptor blocker, 40% angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker, and 10% calcium-channel blockers. All patients received aspirin. Periprocedurally, glycoprotein IIb/IIIa blocker abciximab was given to 10% of the patients.

As shown in Table III, median CRP and mean F VII activity in 27 control patients without CAD were 0.33 (range 0.04–2.98) mg/dl and 123.7 (± 40.6)%, respectively. Median CRP and mean F VII activity in 22 patients with discrete CAD were 0.34 (range 0.02–4.39) mg/dl and 120.7 (± 30.7)%, respectively. Diagnostic angiography led to a significant increase in CRP levels after 16–20 h in patients with discrete CAD (medi-

TABLE II Angiographic and interventional characteristics of the study population according to major adverse coronary events (MACE) and no MACE during a 6-month follow-up

	No MACE n = 64	MACE n = 17	
Multiple site PCI (%)	16 (25)	2 (12)	NS
LAD (%)	27 (42)	8 (47)	NS
RCA (%)	25 (39)	7 (41)	NS
Cx (%)	14 (22)	2 (12)	NS
MG/DG (%)	5 (8)	1 (6)	NS
Diameter stenosis (%)	93 ± 8	87 ± 24	NS
Stent insertion (%)	47 (73)	12 (71)	NS
Min. lumen diameter (mm) (%) ^a	3.1 ± 0.4	2.7 ± 0.4	p = 0.008
Stent length (mm)	13.0 ± 10	12.0 ± 9	NS
Maximal pressure (atm)	13.0 ± 4	14.4 ± 3	NS
Residual stenosis (%)	3.0 ± 9	4.6 ± 8	NS
Angiographic stenosis (>50)			
One vessel (%)	34 (53)	9 (54)	
Multivessel (%)	30 (47)	8 (46)	
Type stenosis			
A (%)	8 (13)	1 (6)	NS
B (%)	44 (69)	11 (65)	NS
C (%)	12 (18)	5 (29)	NS

* Minimal lumen diameter post PCI.

Abbreviations: PCI = percutaneous coronary intervention, LAD = left anterior descending, RCA = right coronary artery, Cx = circumflex, MG/DG = left marginal branch/left lateral (diagonal) branch, NS = not significant.

TABLE III (A) Pre- and postprocedural values of C-reactive protein (CRP) and factor VII (F VII) activity in patients undergoing percutaneous coronary intervention (PCI) according to the two groups (MACE or No MACE) and patients undergoing angiography only, having no coronary artery disease (CAD) (control group) or discrete CAD. (B) C-reactive protein values and F VII activity before and 6 months after PCI in 28 patients according to whether they did or did not have MACE

(A)	CRP preprocedure		CRP post procedure		p Value	F VII preprocedure		F VII post procedure		p Value
	Median	Range	Median	Range		Mean	SD	Mean	SD	
Angiography										
Control, n = 27	0.33	0.04–2.98	0.34	0.02–2.55	0.23	123.74	40.58	125.96	40.67	0.65
Discrete CAD, n = 22	0.34	0.02–4.39	0.45	0.10–4.01	0.012	120.74	30.67	116.04	32.87	0.20
Coronary intervention										
All patients with CAD, n = 81	0.43	0.03–4.82	0.66	0.02–7.72	<0.001	121.47	30.49	117.12	30.26	0.20
No MACE, n = 64	0.41	0.03–4.82	0.64	0.02–7.72	<0.001	122.56	32.64	116.56	30.02	0.13
MACE, n = 17	0.67	0.05–1.34	1.03	0.27–2.71	0.005	117.31	20.77	119.31	32.36	0.74
(B)	CRP preprocedure		CRP at 6 months			F VII preprocedure		F VII at 6 months		
All patients with CAD	0.38	0.05–1.05	0.25	0.04–1.25	0.03	120.77	22.28	123.36	25.83	0.50
No MACE, n = 19	0.32	0.05–1.00	0.22	0.04–0.65	0.02	118.17	22.93	111.5	43.55	0.58
MACE, n = 9	0.41	0.05–0.96	0.36	0.06–1.25	0.41	126.88	22.46	123.66	12.65	0.69

Abbreviations: MACE = major adverse coronary events, SD = standard deviation.

TABLE IV Multivariate analysis of important cofounders for restenosis. C-reactive protein and the minimal lumen diameter post percutaneous coronary intervention remain isolated risk factors for restenosis

Variable	OR	95% CI		p Value
		Lower	Upper	
Thienopyridines	2.843	0.1774	45.595	0.46
LDPPCI	0.0514	0.0039	0.6805	0.02
Statins	0.6298	0.0831	4.7731	0.65
CRP Tertile 1	0.0445	0.0038	0.5224	0.01
CRP Tertile 2	0.1410	0.0155	1.2872	0.08
Type A Stenosis	0.0907	0.0034	2.4019	0.15
Type B Stenosis	0.5982	0.0861	4.1583	0.60

CRP tertiles 1 & 2 OR versus tertile 3.

Type A & B stenosis OR versus type C.

Abbreviations: LDPPCI = lumen diameter post percutaneous coronary intervention, CI = confidence interval, OR = odds ratio.

an 0.45, range 0.10–4.01 mg/dl, $p = 0.012$), whereas patients without CAD had no significant increase of CRP after angiography (median 0.34, range 0.02–2.55 mg/dl). Basal median CRP level in patients undergoing PCI suffering no MACE ($n = 64$) was 0.41 (range 0.03–4.82) mg/dl. Basal median CRP level in patients undergoing PCI suffering from MACE ($n = 17$) was 0.67 (range 0.05–1.34) mg/dl. There was a significant difference in basal CRP levels between patients who had undergone PCI suffering from MACE and patients without CAD ($p = 0.017$). Percutaneous coronary intervention increased CRP levels significantly after 16–20 h, both in patients with or without MACE (median 1.03, range 0.27–2.71 mg/dl; and 0.64, 0.02–7.72 mg/dl, respectively). Factor VII activity was not different in patients undergoing PCI than in those who did not have or only had discrete CAD: 64 patients without MACE in the follow-up period had mean levels of $122.6 (\pm 32.6)\%$, whereas patients suffering from MACE had $117.3 (\pm 20.8)\%$. Neither angiography alone nor PCI significantly influenced F VII activity within 16–20 h: control ($n = 27$) $125.9 (\pm 40.7)\%$; patients with discrete CAD ($n = 22$) $116.0 (\pm 32.8)\%$; PCI without MACE ($n = 64$) $116.6 (\pm 30.0)\%$; PCI with MACE ($n = 17$) $199.3 (\pm 32.3)\%$ (Table IV, Fig. 1).

Percutaneous coronary intervention significantly decreased CRP levels after 6-month follow-up in patients without MACE (from median 0.32, range 0.05–1.05 mg/dl, to median 0.22, range 0.04–0.65 mg/dl; $p = 0.02$; $n = 19$). In contrast, PCI in patients suffering from MACE led to no change in CRP levels within 6 months (from median 0.41; range 0.05–0.96 mg/dl, to median 0.36; range 0.06–1.25 mg/dl; $n = 9$) (Fig. 2). Factor VII activity did not change significantly over a 6-month period. Tertiles of CRP levels independently predicted clinical restenosis. After 6-month follow-up, clinical restenosis developed in 33.3% of patients with the highest CRP levels (0.7–4.8 mg/dl), in 16.6% of patients with second tertile CRP levels (0.23–0.69 mg/dl), and in 7.4% of patients with lowest tertile CRP levels (0.0–0.22 mg/dl). There was a significant difference in the restenosis rate between patients from the first and the third tertile ($p = 0.018$) (Fig. 3). As shown by multivariate

FIG. 1 Box plots of pre- (□) and postinterventional (■) C-reactive protein (CRP) values and factor VII (F VII) activity. MACE = major adverse coronary events.

FIG. 2 C-reactive protein (CRP) plasma levels decrease within 6 months in patients after successful percutaneous coronary intervention (from median 0.32, range 0.05–1.00 mg/dl, to median 0.22; range 0.04–0.65 mg/dl; $p = 0.02$; $n = 19$), but remain unchanged in patients suffering from major adverse coronary events (MACE) (from median 0.41, range 0.05–0.96 mg/dl, to median 0.36, range 0.06–1.25 mg/dl; $n = 9$). □ pre intervention, ■ post intervention 6 months.

FIG. 3 Incidence of major adverse coronary events (MACE) by tertiles of C-reactive protein (CRP). First tertile (0–0.22 mg/dl), second tertile (0.23–0.69 mg/dl), third tertile (0.70–4.80 mg/dl). Overall $p = 0.064$, tertile I vs. tertile II not significant (NS); tertile II vs. tertile III NS; tertile I vs. tertile III $p = 0.018$.

analysis (Table IV), the only predictive parameter for development of clinical restenosis within 6 months besides preprocedural CRP levels was the lumen diameter post PCI. There was no association between F VII activity and clinical outcome after PCI.

Discussion

In this prospective clinical study, we provide further evidence that an increased baseline plasma level of CRP predicts worse clinical outcome in patients undergoing PCI. There was a linear correlation between CRP levels and the incidence of MACE, as defined by angiographically documented restenosis, need for CABG, myocardial infarction, or death. In contrast, F VII activity was no predictor of complications after PCI. This is the first study to show that diagnostic angiography leads to an increase in plasma CRP levels in patients with CAD but not in patients without angiographically detectable coronary atherosclerosis. Another previously unreported finding is that successful PCI is associated with a decrease in plasma CRP levels after a follow-up of 6 months, whereas CRP levels remain unaffected in patients suffering from MACE.

The contribution of inflammation to unstable CAD is well established, whereas the role of CRP measurement in patients with stable angina pectoris is still under debate. A large study including 2,554 patients with angina but no myocardial infarction confirmed a weak correlation between CRP plasma levels and extent of CAD,³ whereas a recently published study of 200 patients with stable angina pectoris or pathologic exercise test failed to show any correlation between CRP plasma levels and presence of coronary atherosclerosis.⁴ Our results show that systemic levels of this inflammatory marker are increased in patients with CAD compared with patients without any angiographically detectable coronary atherosclerosis, but this increase failed to reach statistical significance.

In contrast, preprocedural CRP levels predict a clinical restenosis rate not only in patients with unstable but also in those with stable angina pectoris. Our findings confirm and extend recently published studies by Buffon *et al.*,⁵ Gaspardone *et al.*,⁶ and de Winter *et al.*⁷ Cut-off values found in our study are in good accordance with previously published data in the above-mentioned investigations. For example, Buffon *et al.* calculated cut-off values of 0.28 and 0.82 mg/dl for tertiles analyses, similar to our reported tertile thresholds of 0.23 and 0.70 mg/dl, respectively.

Diagnostic angiography increased CRP levels within 16–20 h in patients with CAD even when no PCI had been performed. As this phenomenon was not seen in patients without coronary atherosclerosis, this may reflect the increased reactivity of dysfunctional endothelial, smooth muscle, or peripheral mononuclear cells to produce inflammatory cytokines such as IL-6, which is known to stimulate hepatic CRP production. C-reactive protein itself has several proinflammatory effects: it enhances tissue factor expression in monocytes, promotes endothelial release of endothelin-1, and decreases nitric oxide production in cultured endothelial cells;⁸ CRP itself

might therefore promote atherosclerosis and restenosis. Long-term effects of PCI on systemic CRP levels have not been investigated so far. In our study, the minimal lumen diameter and CRP are independent risk factors for restenosis. In contrast to patients without MACE during a 6-month follow-up period, CRP levels remain high in those suffering from MACE, independent of drug therapy including statins.⁹

Factor VII activity is an easily measurable clotting parameter in clinical routine but does not necessarily reflect activated F VII antigen. It is a measure of the whole amount of activated and nonactivated VII antigen. Therefore, F VII activity is a value of antigen production rather than antigen activation and reflects the susceptibility to the formation of thrombin. No correlation between F VII activity and the extent of coronary atherosclerosis or restenosis after PCI could be found in this study, suggesting that inflammation rather than thrombus activation might be the leading process for restenosis. Our data, however, do not exclude the importance of local expression of tissue factor in the formation of neointima.¹⁰

The lack of repeat angiographic assessment of restenosis is a major limitation of the present study. Nevertheless, clinical restenosis is much more relevant in routine settings than angiographic restenosis, which is seldom assessed in asymptomatic patients. Of importance is the fact that clinical evaluation of MACE was performed in blinded fashion before statistical evaluation. Another important limitation of our investigation is that CRP levels after 6 months could be measured in only 28 patients, as participation of the study did not oblige patients to return for a follow-up visit. However, of 17 patients suffering from MACE, plasma samples were available in 9 patients after 6 months. Two patients died, and three patients were not eligible for follow-up blood sampling because of postoperative state after CABG.

Conclusion

These findings support the concept that plasma CRP plays a central role in the development of restenosis even after elective PCI in patients with stable angina pectoris. Routine measurement of preprocedural CRP levels may help in risk stratification for MACE in such patients and may guide appropriate use of statin therapy even in the absence of hyperlipidemia,¹¹ or new therapeutic devices such as drug-eluting stents known to decrease the incidence of restenosis.

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Images in Cardiology: Unusual Anomalies of the Left Circumflex Artery

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FIG. 1 Coronary angiogram of the left coronary artery in a left anterior oblique (LAO) view with cranial angulation with the left circumflex artery (LCX) originating from the first diagonal branch (DIA) of the left anterior descending artery (LAD).

FIG. 2 Coronary angiogram of the left coronary artery in a LAO view with caudal angulation with the left circumflex artery (LCX) originating from the left anterior descending artery (LAD). A ramus intermedius (RI) branch is also seen.

The most common congenital anomaly of the circumflex artery is origin from the right sinus of Valsalva or right coronary artery.¹ Images show unusual anomalies in a patient who presented with an acute anterior myocardial infarction and underwent successful surgical revascularization. To our knowledge these anomalies have not been previously reported.

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