Clin. Cardiol. 26, 85–90 (2003)

C-Reactive Protein and Rapidly Progressive Coronary Artery Disease—Is There Any Relation?

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Summary

Background: High plasma C-reactive protein (CRP) levels have been associated with an unfavorable outcome in patients with coronary artery disease (CAD), and a direct participation of CRP in the atherosclerotic process has been postulated.

Hypothesis: The aim of this study was to evaluate the possible relationship of high plasma CRP levels with the rapid progression of coronary atherosclerosis (RPCAD).

Methods: In all, 194 patients who were readmitted and underwent repeat coronary angiography because of recurrence of symptoms following successful percutaneous coronary intervention were studied. Median angiographic follow-up time was 6 months. Rapid progression CAD was defined as the presence of a new lesion, > 25% in luminal diameter stenosis, in a previously nondiseased vessel, or deterioration of a known, nontreated lesion by at least 25%.

Results: By multivariate analysis, patients with high plasma CRP levels upon first admission were at higher risk of RPCAD. In particular, odds ration (OR) = 1.8; 95% confidence interval (CI) = 1.3–3.6; p value = 0.02 in patients with CRP = 0.5–2 mg/dl versus patients with CRP < 0.5 mg/dl, and OR = 7.1; 95% CI = 3.8–9.5; p value < 0.001 in patients with CRP > 2 mg/dl versus patients with CRP < 0.5 mg/dl.

Conclusion: Increased plasma CRP levels could possibly identify patients at high risk for the development of RPCAD.

Key words: C-reactive protein, inflammation, progression of atherosclerosis, angiographic study, prognosis, risk factors

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Received: October 12, 2001
Accepted with revision: March 8, 2002

Introduction

Several reports have recently implied the pivotal role of inflammation in the pathogenesis or complications of coronary artery disease (CAD).[1–4] In particular, high plasma C-reactive protein (CRP) levels in either apparently healthy individuals, or in patients with stable or unstable angina, or acute myocardial infarction (MI), have been reported to predict the risk of short- and long-term cardiovascular morbidity or mortality.[5–7] However, the underlying pathophysiologic mechanisms have not yet been clarified.

It has been hypothesized that raised plasma CRP levels could be an epiphenomenon,[4] reflecting the inflammatory response in coronary vessels induced by infective agents (virus, bacteria),[8] or the inflammatory status related to the extent or severity of atherosclerosis.[9, 10] Increased CRP levels have also been associated with the extent of myocardial ischemia[11] or infarction,[12, 13] as well as with the amount or the activity of the circulating cytokines.[14, 15] Notably, recent studies confirming the presence of CRP molecules in coronary atherosclerotic plaques[16, 17] or infarcted myocardial cells[18] make the possibility of a direct participation of CRP in cardiovascular events very tenable. C-reactive protein molecules may induce instability in the atherosclerotic plaques, which predispose to rapid progression of CAD. This mechanism may be involved in the worse prognosis of patients with raised plasma CRP levels.

Despite the mounting evidence, the influence of elevated plasma CRP levels on the angiographic course of CAD has not yet been thoroughly investigated. The aim of this study was to

evaluate the possible association of high plasma CRP levels with the development of rapidly progressing CAD (RPCAD).

Patients and Methods

Study Patients

For the purpose of this angiographic study, 232 patients who were readmitted to our department and underwent repeat coronary angiography (CA) because of recurrence of symptoms, in a median period of 6 months (range 10 days to 12 months) following successful percutaneous coronary intervention (PCI), were evaluated. On initial admission, patients were presented due to stable or unstable angina, or acute MI, and all underwent successful PCI with or without stent implantation.

Sixteen patients who on first admission had either coexisting conditions, which might have interfered with plasma CRP levels (e.g., chronic inflammatory disease), or early acute MI with parallel elevation in creatine phosphokinase (CK)-MB levels (> 2× normal) were excluded. Ten patients with past coronary artery bypass grafts and 12 patients with no available CRP data were additionally excluded. In the former, progression of coronary atherosclerosis could have been affected by surgical injury, or alterations in coronary blood flow due to grafts implantation. Thus, 194 of 232 patients with repeat CA comprised the study population.

Patients' characteristics, clinical information, and PCI data were retrieved from our computerized databank. Of 194 patients, 44 (22.7%) had developed RPCAD in 59 not previously treated vessels during the angiographic follow-up. Patients were divided into two groups: a group of 150 patients without RPCAD and a group of 44 patients with RPCAD on repeat angiographic studies.

Percutaneous Coronary Intervention Procedure

Percutaneous coronary intervention was performed by standard techniques. Stents were implanted as a bailout procedure after failed simple PCI, or due to the absence of optimal angiographic result, or electively.

Heparin 10,000 IU was routinely administered just before the procedure and consequently for 24 to 48 h, with regular activating clotting time monitoring. All patients received aspirin (100 to 325 mg/day) starting at least 24 h before PCI and continuing indefinitely. Ticlopidin (250 mg b.i.d.) was started immediately after PCI with stent implantation and continued for 4 weeks thereafter.

Definitions

Percutaneous coronary intervention was considered successful if there were no procedural adverse events such as death, MI, or need for urgent cardiac surgery, and if the visually estimated angiographic residual stenosis was < 30%, with a Thrombolysis in Myocardial Infarction (TIMI) grade III flow in the dilated vessel, immediately after angioplasty.

Rapidly progressing CAD was defined as the presence of a new lesion > 25% in luminal diameter stenosis in a previously nondiseased vessel, or deterioration of a known, nontreated lesion by at least 25%.[19]

Collection of Blood Samples and Laboratory Assays

Upon first admission, blood samples were obtained to determine CRP, lipids profile, total CK-MB isoenzyme (mass), and other biochemical indices. These constitute the standard laboratory tests in all patients who were admitted at our department because of suspected CAD.

The analysis of plasma CRP was done using a semi-quantitative (of low sensitivity) analytic method (CRP-Slidex, Bio Merieux, France), which specifies three levels of CRP plasma levels: < 0.5 mg/dl, 0.5–2 mg/dl, and > 2 mg/dl. In our laboratory, the reproducibility of the method was 100% and the variability was ± 0.07, ± 0.11, and ± 0.19 for the < 0.5 mg/dl, 0.5–2 mg/dl, and > 2 mg/dl assays, respectively.

Coronary Angiography and Angiographic Analysis

All catheterizations were performed by the femoral approach and included at least five and two views for the left and right coronary system, respectively. Two independent and experienced angiographers, blinded to the study, performed vessel and lesion measurements using computerized quantitative CA analysis. All measurements were performed on end-diastolic frames. The reference and the minimal lumen diameters were measured on identical views on first and second CA. The difference in percent diameter stenosis, at the same points in the coronary arteries, between the two CA was calculated in the determination of the rapidly developed atheromatic burden. Values were calculated as the mean score given by the two observers. Intra- or interobserver variability was < 10%.

The Hospital Ethics Committee approved the study and informed consent was obtained from all patients before CA.

Statistical Analysis

Values were expressed as mean ± standard deviation (SD). Comparisons of continuous variables were made by *t*-test, or Mann-Whitney U test, as appropriate. Associations between two categorical variables were tested by chi-square test or Fisher's exact test, as appropriate.

Event-free curves were analyzed by the Kaplan-Meier method, and the log-rank test was used for comparison among curves. Univariate Cox regression analysis was constructed to identify univariate predictors of RPCAD. All baseline (first admission) demographic, clinical, biochemical, or procedural parameters, as well as medical treatment between the two hospitalizations, were evaluated. Subsequently, all variables with a $p < 0.1$ were included as covariates in a Cox regression multivariate model to determine the independent predictors of RPCAD. All tests were two-tailed, and a $p < 0.05$ was considered as the level of statistical significance. Statistical analysis was

TABLE I Baseline demographic, clinical, and C-reactive protein (CRP) data between patients without or with rapidly progressive coronary artery disease (RPCAD)

	Patients without RPCAD (n = 150)	Patients with RPCAD (n = 44)	p Value
Age (years), mean ± SD	58.8 ± 8.9	57.5 ± 9.2	0.4
Male gender (%)	82.0	79.5	0.7
Hypertension (%)	46.7	40.9	0.5
Smoking (%)	61.3	54.5	0.4
Hypercholesterolemia (%)	46.7	54.5	0.4
Diabetes mellitus (%)	14.7	15.9	0.8
Family history of CAD (%)	30.7	34.1	0.7
Stable angina (%)	19.3	15.9	0.6
Unstable angina (%)	30.0	40.9	0.2
Myocardial infarction (%)	50.7	43.2	0.5
PCI with stent (%)	74.0	45.5	< 0.001
LVEF (%), mean ± SD	51.1 ± 8.4	50.5 ± 9.0	0.7
CRP mg/dl			
< 0.5 (%)	43.3	9.1	
0.5–2 (%)	46.0	40.9	< 0.001
> 2 (%)	10.7	50.0	

Abbreviations: SD = standard deviation, CAD = coronary artery disease, PCI = percutaneous coronary intervention, LVEF = left ventricular ejection fraction.

performed with the Statistical Package for Social Sciences (SPSS) software (release 10.0, SPSS, Inc., Chicago, Ill., USA).

Results

Patients' demographics, and clinical, CRP, and PCI data at first hospitalization are summarized in Table I. Patients with RPCAD on repeat CA had significantly higher plasma CRP levels upon first admission and underwent significantly fewer PCI procedures with stent implantation during this hospitalization. There were no other statistically significant differences between the two groups.

Several drugs were prescribed after PCI procedures. Aspirin was prescribed in 98.3 and 98.7% of patients with or without RPCAD, respectively (p = 0.9). Significantly more patients without RPCAD on repeat CA received ticlopidin during the follow-up period, obviously due to the performance of more PCI procedures with stent implantation in these patients. The rest medication did not differ between the two groups (data not presented).

Comparisons of clinical data at rehospitalization are presented in Table II. It is interesting that patients with RPCAD were readmitted earlier than patients without RPCAD, and more frequently because of acute coronary syndromes.

The angiographic characteristics of the 59 vessels with RPCAD are presented in Table III. Between the two CA, there was an increase in the mean lumen diameter stenosis from 22 to 79% (p value < 0.001) at the affected sites, without significant alteration in the reference lumen diameter (p value =

TABLE II Clinical data at rehospitalization between patients without or with rapidly progressive coronary artery disease (RPCAD)

	Patients without RPCAD (n = 150)	Patients with RPCAD (n = 44)	p Value
Interval between first and second admission in days, mean ± SD	192.8 ± 62.1	115.2 ± 77.9	< 0.001
Interval between readmission and CA in days, mean ± SD	4.5 ± 1.5	4.5 ± 1.3	1.0
Qualifying event upon readmission			
Stable angina [a] (%)	54.0	29.5	0.004
Unstable angina (%)	22.7	43.2	0.007
Myocardial infarction (%)	16.0	22.7	0.3
Acute coronary events (%)	38.7	65.9	0.001
Other events [b] (%)	7.3	4.6	0.3

[a] Stable angina or positive exercise test.

[b] Congestive heart failure, syncope, or cardiac arrhythmia.

Abbreviations as in Table I.

TABLE III Angiographic characteristics of the 59 vessels with rapidly progressive coronary artery disease

LAD (%)	25.3
LCx (%)	15.1
RCA (%)	24.1
Branch [a] (%)	35.5
Minimal lumen diameter on first CA (mm)	1.99 ± 0.82
Vessel stenosis on first CA (%)	22.1 ± 11.5
Minimal lumen diameter on second CA (mm)	0.61 ± 0.3
Vessel stenosis on second CA (%)	79.3 ± 15.9
Reference lumen diameter on first CA (mm)	2.71 ± 0.55
Reference lumen diameter on second CA (mm)	2.73 ± 0.51

[a] Diagonal, OM 1, or OM 2.

Abbreviations: LAD = left anterior descending, LCx = left circumflex, RCA = right coronary artery, OM = obtuse marginal, CA = coronary angiography.

0.99). Four patients with plasma CRP levels < 0.5 mg/dl upon first admission had developed RPCAD between the two hospitalizations (5.8%; 4/69). However, 18 (20.7%; 18/87) and 22 (57.9%; 22/38) patients with plasma CRP levels 0.5–2 mg/dl and > 2 mg/dl, respectively, had developed RPCAD on repeat CA. Although there were no statistically significant differences concerning the baseline characteristics between patients who underwent simple PCI or PCI with stent implantation, the occurrence of RPCAD was more prominent in the former than the latter (38.1; 24/63 vs. 15.3%; 20/131, respectively; p value < 0.001).

Survival curves (Fig. 1) showed that plasma CRP levels, obtained upon first admission, were significantly associated with the risk of RPCAD development during the entire period between the two sequential CA. By univariate Cox regression analysis, only baseline plasma CRP levels, PCI procedure with stent implantation, and unstable angina at first hospitalization were significantly related to the incidence of RPCAD. By multivariate Cox regression analysis, baseline plasma CRP levels and PCI with stent implantation were found to be significantly and independently associated with the incidence of RPCAD (Table IV).

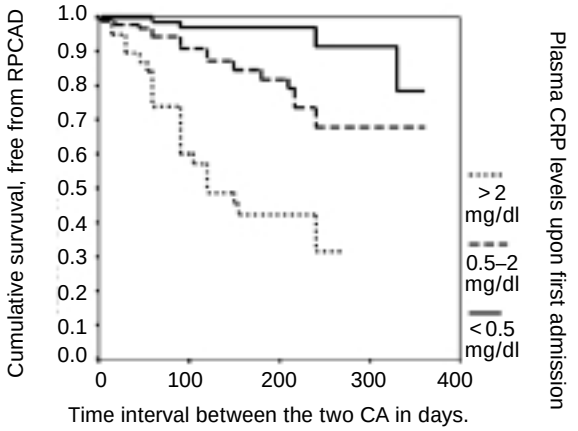

FIG. 1 Survival free from rapidly progressive coronary artery disease (RPCAD) among the 194 studied patients according to plasma C-reactive protein (CRP) levels upon first admission. Log rank x^2 = 7.8, p value = 0.005 among 0.5–2 mg/dl vs. < 0.5 mg/dl; log rank x^2 = 21.4, p value < 0.001 among > 2 mg/dl vs. 0.5–2 mg/dl; log rank x^2 = 44.7, p value < 0.001 among > 2 mg/dl vs. < 0.5 mg/dl. CA = coronary angiography.

Discussion

C-reactive protein is a nonspecific but sensitive acute phase reactant.[20] The secretion of CRP is induced by cytokines (especially interleukin-6), which are produced by jeopardized tissues and activated macrophages.[21, 22] Cytokines stimulate the liver in CRP production.[20] In vitro, CRP displays both anti-inflammatory and proinflammatory effects.[23, 24]

Our study showed that high plasma concentrations of CRP may predict the risk of future development of RPCAD. Several previous prospective studies have constantly shown the independent association of high plasma CRP levels with increased cardiovascular mortality and morbidity.[5, 7] However, to the best of our knowledge, the present study is the first that has shown a positive relationship of high plasma CRP levels with the angiographically documented progression of coronary atherosclerosis. This positive association was statistically significant by both univariate and multivariate analysis.

TABLE IV Univariate and multivariate predictors of rapidly progressive coronary artery disease

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Unstable angina [a]	1.8 (0.99–3.4)	0.05	1.1 (0.6–2.0)	0.8
PCI with stent	0.3 (0.2–0.6)	< 0.001	0.4 (0.2–0.8)	0.006
CRP upon first admission				
0.5–2 mg/dl vs. < 0.5 mg/dl	2.1 (1.4–4.8)	0.01	1.8 (1.3–3.6)	0.02
> 2 mg/dl vs. 0.5–2 mg/dl	4.0 (2.1–7.6)	< 0.001	3.3 (1.7–6.6)	< 0.001
> 2 mg/dl vs. < 0.5 mg/dl	7.7 (5.1–12.3)	< 0.001	7.1 (3.8–9.5)	< 0.001

[a] At first hospitalization.

Abbreviations: OR = odds ratio, CI = confidence interval, PCI = percutaneous coronary intervention, CRP = C–reactive protein.

The potential mechanism of this association may involve a direct influence of CRP molecules on the coronary atheromatic plaques.[4, 17, 18] Recently, a published study has shown the absence of CRP molecules in the walls of normal coronary arteries, but their colocalization with activated complement in thickened intimae, just beneath the endothelium.[17] Furthermore, the proinflammatory effect of CRP molecules includes the ability of ligand-bound CRP to activate the complement system.[25] Consequently, CRP may induce local activation of the complement system in the coronary tree,[4, 17] which may generate vascular injury via several mechanisms: aggregation and degranulation of neutrophils,[26] enhancement of clotting by induction of tissue factor expression,[27] or direct damage of endothelial cells by insertion into the cell membranes.[4, 28] This vascular inflammatory injury may predispose to the growth of the atheromatous plaques and to the development of RPCAD. Although the ability of CRP to initiate the terminal complement pathway has been argued,[29] CRP molecules could contribute to the progression of atherosclerosis by other mechanisms, including the induction of monocytes in tissue factor expression.[30]

While the direct participation of CRP molecules in the development of RPCAD could not be excluded, elevated plasma CRP level may constitute an epiphenomenon in these patients. In particular, high plasma CRP levels may reflect the inflammation related to atherosclerotic process. Atherosclerosis could be considered a chronic inflammatory disease, like rheumatoid arthritis that develops in response to some metabolic, physical, infectious, or environmental factors. Acute exacerbation of inflammation, induced by these factors, may have a role in elevating the plasma CRP levels, in activating arterial endothelium, in destabilizing the fibrous cap, and enhancing the risk of atherosclerosis progression and acute thrombosis. Identification of the possible triggering factors (e.g., *Chlamydia pneumonia*) may provide insight for the causative management and prevention (e.g., possible favorable effect of antibiotics) of RPCAD.

In the present study, patients who underwent PCI with stent implantation were at lower risk of developing RPCAD. It is possible that accumulation and activation of platelets and inflammatory cells contribute, via the secretion of several growth factors, to the rapid progression of the previously slow inflammatory process. Dual antiplatelet therapy (aspirin-ticlopidin) prescribed in the stented patients probably contributed to a more potent prevention of activated platelet aggregation on endothelial surface, resulting in the deceleration of RPCAD occurrence.

Limitations of the Study

The present study is a retrospective analysis of prospectively collected data from patients who underwent PCI and subsequently repeat CA because of recurrence of symptoms; thus, a bias regarding patients studied could not be excluded. Consequently, the association of high plasma CRP levels with RPCAD may apply only in such patients and could not be extrapolated to the entire CAD population. However, the observation of a positive association of high CRP with RPCAD seems to be in concordance with many previous nonangiographic studies, which have confirmed the unfavorable prognosis of patients with CAD with high plasma CRP levels.[5, 7]

Another limitation is the semiquantitative assessment of CRP. This method of CRP measurements is of low sensitivity and produces a rough grouping of patients, with the major differences between patients with and without RPCAD in the extreme values of CRP. However, the aim of this study was not to determine a cut-off point for circulating CRP associated with increased risk of RPCAD. Large prospective trials, with higher sensitivity CRP assay, are essential to elucidate this issue. The purpose of this study was to approach a question of significant current interest. This study tried to offer insight into one of the potential mechanisms underlying the association between elevated plasma levels of CRP and the risk of CAD. Previous nonangiographic studies using more sensitive assays have determined more accurate cut-off points for increased risk of future cardiovascular events.[5]

Conclusions

Patients with CAD and elevated plasma levels of CRP may be at high risk of rapid progression of coronary atherosclerosis. The underlying mechanisms are only speculative, but this finding may partly explain the increased short- and long-term morbidity and mortality in patients with elevated plasma CRP levels, documented by several previous studies. Our results, if validated by other large specifically designed prospective studies, may improve risk stratification and management of patients with CAD.

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