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# C-Reactive Protein Is a Marker for a Complex Culprit Lesion Anatomy in Unstable Angina

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**Summary**

*Background:* The putative theory is that the clinical syndrome of unstable angina is caused by rupture of the atherosclerotic plaque with superimposed thrombus formation. It is characterized by angiographically complex coronary lesions in the majority of patients.

*Hypothesis:* This study aimed at assessing the correlation between C-reactive protein (CRP) and the complexity of culprit coronary lesions in unstable angina.

*Methods:* We identified culprit lesion complexity in 96 patients with unstable angina and normal creatine kinase (CK) and CK-MB mass. Serum concentrations of CRP ($N < 5.0$ mg/l) and cardiac troponin T (cTnT; $N < 0.1$ ng/ml) were measured on admission.

*Results:* There was a trend toward a higher grade of anatomical complexity of the culprit lesion in patients with elevated CRP ($p = 0.007$) and cTnT levels ($p = 0.027$). Patients who had intermediate- or high-grade lesion severity had a higher level of CRP ($8.5 \pm 5.7$ mg/l) and cTnT ($0.118 \pm 0.205$ ng/ml) on admission than those who had normal or low-grade lesions ($5.7 \pm 4.0$ mg/l, $0.017 \pm 0.021$ ng/ml, respectively); Mann-Whitney U, $p = 0.002$ and $p < 0.001$, respectively. Furthermore, the likelihood of having intermediate- or high-grade complexity of the culprit lesion was higher when CRP levels were elevated in all patients ($p = 0.007$, odds ratio [OR] = 4.286; 95% confidence interval [CI] 1.492–12.310) and in those with normal cTnT levels ($p = 0.025$, OR = 3.876; 95% CI 1.185–12.678). Also, higher CRP levels strongly correlated with the need for revascularization interventions ($p < 0.0005$).

*Conclusion:* Elevated CRP level on admission is a marker for anatomic complexity of culprit lesions and need for revascularization interventions in unstable angina.

**Key words:** unstable angina, C-reactive protein, troponin T, culprit lesion

## Introduction

The putative theory is that the clinical syndrome of unstable angina is caused by rupture of the atherosclerotic plaque with superimposed thrombus formation. It is characterized by angiographically complex coronary lesions in the majority of patients.[1] This anatomy often portends high morbidity.[2] Inflammation has been implicated in the pathophysiology of vulnerable coronary plaques. This is evident from histologic studies of coronary lesions demonstrating abundant inflammatory infiltrates (macrophages and lymphocytes) in unstable compared with stable plaques.[3–8] Furthermore, the local inflammatory process in the coronary arteries seems to be expressed systemically by a rise in the levels of the acute phase reactants and cytokines. C-reactive protein (CRP) is a sensitive early marker of inflammation and has been shown to rise several thousandfold in the presence of an inflammatory process in the body.[9, 10] Several studies have examined the association of CRP with acute coronary syndromes. C-reactive protein rise has been reported before[11] as well as during unstable angina episodes[12] even in the absence of evidence of myocardial injury.[13] The CRP rise is unlikely to be related to ischemia-reperfusion injury, since it was absent in patients with variant angina.[14] Clinically, it appears that elevated CRP predicts a poor prognosis in patients with unstable angina, reflected by increased incidence of adverse ischemic cardiac events.[13, 15–17] A new paradigm has emerged suggesting a strong link between CRP levels and inflammatory activity in the culprit lesion. This study was designed to explore the correlation of CRP levels with the degree of culprit lesion angiographic complexity in an unselected group of patients with unstable angina.

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## Methods

### Patients

Consecutive patients admitted to the coronary care unit at the American University of Beirut-Medical Center between November 1998 and September 1999 with the diagnosis of unstable angina pectoris Braunwald class IIIB[18] were screened. Patients with evidence of myocardial infarction (MI) on admission (corresponding electrocardiographic [ECG] changes, abnormal serum levels of lactate dehydrogenase, creatine kinase, or creatine kinase-MB), MI within the past 2 months, pulmonary edema on admission, valvular heart disease, evidence of infection, malignancies, and inflammatory diseases known to cause an acute phase response were excluded. In all, 96 patients (74 men and 22 women) with a mean (± standard deviation) age of 57 ± 10 years, were studied. All patients received aspirin and intravenous heparin as well as combinations of nitrates, calcium-channel blockers, and beta blockers. C-reactive protein and cardiac troponin T (cTnT) were measured 7.7 ± 2.8 h after the onset of symptoms. Creatine kinase and CK-MB were measured on admission and serially at 6, 12, and 24 h after the onset of symptoms. Continuous ECG monitoring was performed on all patients during their stay in the coronary care unit. All patients underwent coronary angiography before discharge from the coronary care unit. The study was in accordance with the Declaration of Helsinki.

### Plasma Protein Assays

*C-reactive protein:* C-reactive protein assay was determined by turbidimetry based on the principle of immunological agglutination (Boehringer Mannheim, Mannheim, Germany). Patients' blood was mixed with goat antihuman anti-CRP antibody to form an antigen/antibody complex. Following agglutination, this was measured turbidimetrically. Standardization was performed according to the manufacturer's guidelines. The lower detection limit was 3 mg/l. Any value < 5.0 mg/l was considered to be normal according to the manufacturer's datasheet.

*Cardiac troponin T:* Cardiac troponin T assay was determined by electrochemiluminescence immunoassay using the sandwich principle (Elecsys Troponin T STAT immunoassay; Roche Diagnostics, Mannheim, Germany). The lower detection limit was 0.01 ng/ml. As recommended by the assay manufacturer, any value < 0.1 ng/ml was taken to be normal.

### Coronary Angiography

Using standard techniques, all patients underwent coronary angiography within 5 days of admission. The angiograms were reviewed independently by two cardiologists blinded to the results of the protein assays. Diseased vessels were defined by the presence of a lesion with ≥ 40% diameter stenosis. Lesions were characterized according to severity of diameter stenosis (< 50%, 50–70%, > 70% or 99%, graded from 1 to 4) and morphology according to the American Heart Association/American College of Cardiology classification[19] (A, B1, B2, or C, graded from 1 to 4). A complexity score of lesion anatomy was assigned according to the sum of the grade of severity of diameter stenosis and morphology of the lesion. The culprit lesions in patients were identified as follows: presence of only one lesion (n = 25), correlation with ST-T changes on ECGs during anginal attacks (n = 15), and correlation with findings on echocardiograms (n = 18). In the remaining patients who had only two lesions with equal complexity scores (n = 8), one of them was arbitrarily chosen to be the culprit. In patients who had two or more different lesions, the one with the highest complexity score was identified as the culprit (n = 5). There were 25 patients who had normal coronary angiograms.

### Statistical Analysis

All statistical analyses were done using a statistical software package (Statistical Package for Social Sciences 7.5 for Windows, SPSS, Inc., Chicago, Ill., USA). Results are expressed as mean ± standard deviation. Since continuous variables did not assume a normal distribution, the Mann-Whitney U nonparametric test was used to compare such variables. Chi-square and Fisher's exact tests were used for comparison of discrete variables. Multiple logistic regression analysis was used to determine factors independently correlated with intermediate- or high-grade complexity of the culprit lesion. Statistical comparisons were two-tailed, and a p value of $< 0.05$ was considered statistically significant.

## Results

### Clinical Characteristics

The mean age of the 96 patients enrolled in the study was 57 years (range 33–86). There were 74 (77.1%) men and 26 (22.9%) women. Their clinical characteristics are shown in Table I. Smoking and hyperlipidemia were the most common risk factors (present in 64.6 and 59.4% of the patients, respectively).

TABLE I Demographic characteristics of the study patients (n = 96)

| | |
|---|---|
| Age (years) (mean ± SD) | 57 ± 10 |
| Male (%) | 74 (77.1) |
| Female (%) | 26 (22.9) |
| Family history of CAD (%) | 56 (58.3) |
| Smoking history (%) | 62 (64.6) |
| Diabetes mellitus (%) | 19 (19.8) |
| Hypertension (%) | 24 (25) |
| Hyperlipidemia (%) | 57 (59.4) |
| History of CAD (%) | 38 (39.6) |
| Previous revascularization (PTCA/CABG) (%) | 16 (16.7) |

*Abbreviations:* CAD = coronary artery disease, PTCA = percutaneous transluminal coronary angioplasty, CAGB = coronary artery bypass graft, SD = standard deviation.

TABLE II Distribution of patients according to angiographic findings

| | |
|---|---|
| Distribution of coronary artery disease | |
| No disease (%) | 25 (26.0) |
| Single-vessel (%) | 27 (28.1) |
| Double-vessel (%) | 23 (24) |
| Triple-vessel (%) | 21 (21.9) |
| Location of the culprit lesion | |
| Left anterior descending (%) | 42 (43.8) |
| Circumflex (%) | 15 (15.6) |
| Right coronary artery (%) | 14 (14.6) |
| Complexity of culprit lesion anatomy | |
| Low grade (%) | 9 (9.4) |
| Intermediate grade (%) | 32 (33.3) |
| High grade (%) | 30 (31.3) |

TABLE III Grade of complexity of the culprit lesion according to C-reactive protein (CRP) status

| | Normal CRP (< 5.0 mg/l) n = 19 | Elevated CRP (≥ 5.0 mg/l) n = 77 | Total | p Value |
|---|---|---|---|---|
| Complexity of lesion | | | | 0.007 |
| Normal (%) | 8 (42.1) | 17 (22.1) | 25 (26) | |
| Low grade (%) | 4 (21.1) | 5 (6.5) | 9 (9.4) | |
| Intermediate grade (%) | 5 (26.3) | 27 (35.1) | 32 (33.3) | |
| High grade (%) | 2 (10.5) | 28 (36.4) | 30 (31.3) | |

### Findings at Angiography

The mean time to angiography from admission was approximately 3 days. Twenty-five patients (26.0%) had normal coronary arteries on angiography, and 27 (28.1%), 23 (24%), and 21 (21.9%) had single-, double-, or triple-vessel coronary disease, respectively. The culprit lesions were classified into three categories according to the score of anatomical complexity, whether low (a score of 3 or less), intermediate (a score of 4 or 5), or high grade (a score of 6 or more). Table II shows the distribution of patients according to angiographic findings.

### C-Reactive Protein Levels and Relation to Culprit Lesion Severity

The CRP values ranged from 3.0 to 28.8 mg/l (mean 7.5, standard deviation 5.3 mg/l); they were elevated (≥ 5.0 mg/l) in 77 (80.2%) patients. Their baseline characteristics showed no statistically significant difference when compared with the rest of the patients. The distribution of the grade of culprit lesion complexity according to CRP status is illustrated in Table III. There was a trend toward a higher grade of anatomical complexity of the culprit lesion in patients with elevated CRP levels (p = 0.007). Even after excluding patients with normal coronary angiography, the relationship remained significant (p = 0.012; Fig. 1). The probability of having an intermediate- or high-grade complexity of the culprit lesion was significantly higher among patients with elevated than in those with normal CRP levels (p = 0.007, OR = 4.286; 95% CI 1.492–12.310) and this was observed even among patients with normal cTnT assay (p = 0.025, OR = 3.876; 95% CI 1.185–12.678) (Fig. 2). Furthermore, patients who had intermediate- or high-grade lesion severity had a higher level of CRP (8.5 ± 5.7 mg/l) on admission than those who had normal or low-grade lesions (5.7 ± 4.0 mg/l; Mann-Whitney U; p = 0.002), and this remained significant after excluding patients with normal angiography. Of the 30 patients with high-grade complexity of the culprit lesion, 28 had elevated CRP levels, and all those who had elevated cTnT had concomitant elevation of the CRP levels. Furthermore, only 2 of the 32 patients with intermediate-grade complexity of the culprit lesion had elevated cTnT despite normal CRP levels. The positive predictive value of elevated CRP as a marker for diseased coronaries was 78%. To account for differences in baseline characteristics, a multiple logistic regression analysis model including age, gender, smoking history, hypertension, diabetes mellitus, hyperlipidemia, family history, and the presence of previous coronary artery disease

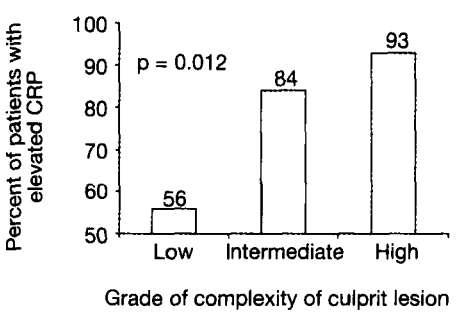


FIG. 1 Correlation of C-reactive protein (CRP) and culprit lesion complexity expressed as percentage of patients with elevated CRP by grade of anatomical complexity of the culprit lesion. Trend was evaluated using the chi-square test.

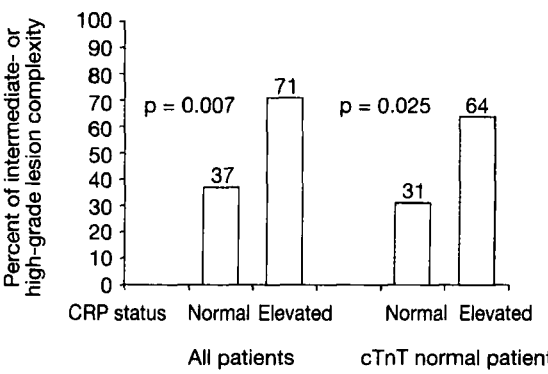


FIG. 2 Percentage of intermediate- or high-grade lesion complexity by C-reactive protein (CRP) status in all patients and in those with normal cardiac troponin T (cTnT) assay. Comparison made by Fisher's exact test.

TABLE IV Grade of complexity of the culprit lesion according to cardiac troponin T (cTnT) status

| | Normal cTnT (< 0.1 ng/ml) n = 74 | Elevated cTnT (≥ 0.1 ng/ml) n = 22 | Total | p Value |
|---|---|---|---|---|
| Complexity of lesion | | | | 0.027 |
| Normal (%) | 23 (31.1) | 2 (9.1) | 25 (26.0) | |
| Low grade (%) | 9 (12.2) | | 9 (9.4) | |
| Intermediate grade (%) | 20 (27.0) | 12 (54.5) | 32 (33.3) | |
| High grade (%) | 22 (29.7) | 8 (36.4) | 30 (31.3) | |

was used. The only independent predictor of intermediate- or high-grade complexity of the culprit lesion was the presence of elevated CRP (OR = 3.9; 95% CI 1.2–13.4; p = 0.027).

### Troponin T levels and Relation to Culprit Lesion Severity

Cardiac troponin T values ranged from 0.010 to 0.999 ng/ml (mean 0.082, standard deviation 0.172 ng/ml). They were elevated (≥ 0.1 ng/ml) in 22 (22.9%) patients. These patients showed no significant differences in their characteristics compared with the rest of the patients. The distribution of the grade of culprit lesion complexity according to cTnT status is illustrated in Table IV. There was a trend toward a higher grade of anatomical complexity of the culprit lesion in patients with elevated cTnT levels (p = 0.027). Also, patients who had intermediate- or high-grade lesion severity had a higher level of cTnT (0.118 ± 0.205 ng/ml) on admission than those who had normal or low-grade lesions (0.017 ± 0.021 ng/ml; Mann-Whitney U, p < 0.001), and this remained significant after excluding patients with normal angiography.

## Clinical Outcome

There was no cardiac death during the short period of follow-up that was about 2 weeks for most of our study patients. One patient (1%) had an episode of atrial fibrillation, and three (3.1%) developed MI while on therapy. There were 46 (47.9%) revascularizations, listed in Table V. Patients who underwent revascularization had a higher level of CRP (9.4 ± 6.3 mg/l) and troponin T (0.132 ± 0.227 ng/ml ) on admission than those who were discharged on medical therapy (5.8 ± 3.5 mg/l and 0.037 ± 0.073 ng/ml, respectRely; Mann-Whitney U, p < 0.001). Furthermore, the probability of requiring a revascularization procedure increased with rising concentrations of CRP (Fig. 3).

TABLE V Events during hospitalization

| | |
|---|---|
| Events on treatment | |
| Cardiac death (%) | 0 (0) |
| Myocardial infarction (%) | 3 (3.1) |
| Arrhythmias (%) | 1 (1.0) |
| Total (%) | 4 (4.1) |
| Revascularization | |
| PTCA (%) | 29 (30.2) |
| CABG (%) | 17 (17.7) |
| Total (%) | 46 (47.9) |

Abbreviations as in Table I.

## Discussion

The contribution of inflammation to the pathogenesis of the syndrome of unstable angina is emerging as a profoundly relevant factor. Recent molecular biological studies have elucidated the relation between cytokines evoked by activated macrophages and plaque vulnerability.[3–8] Inflammation causes imbalance between fibrous cap degradation and repair.[20] Several clinical observations have established a quantitative relationship between the degree and level of inflammation and the clinical outcome in symptomatic and asymptomatic patients with coronary artery disease.[16, 17, 21] However, data correlating the markers of inflammation with angiographic anatomy are scarce. Our study confirms previous observations relating inflammation and need for revascularization.[13] It also provides new knowledge pertaining to the link between inflammation and coronary events. We noted significant correlation between elevated CRP levels and the grade of the culprit lesions' anatomical complexity in patients with unstable angina. Our findings also confirm the observed relation between cTnT levels (a marker of ischemic myocardial damage) and complexity of culprit lesions.[22] Thus, a strong interaction between plaque inflammation and thrombosis seems to be the basis of unfavorable plaque transformation, anatomic complexity, and consequent adverse clinical event. Higher occlusion rates and worse prognosis have been reported in patients with elevated cTnT, even when treated aggressively by interventional strategy.[23] The fact that platelet receptor blockers

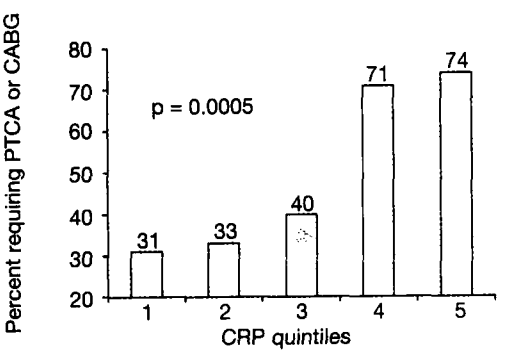


FIG. 3 Correlation of C-reactive protein (CRP) concentration and need for revascularization expressed as percentage of patients requiring percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG) by quintiles of CRP concentrations. Trend was evaluated by chi-square test.

confer better protection in patients with elevated cTnT[24] is further evidence for the heightened thrombotic state triggered by inflammation.

## Conclusion

We suggest that patients with unstable angina be additionally stratified according to markers of inflammation. These markers seem to predict complex plaque angiographic anatomy, and hence the potential for accelerated plaque progression, remodeling, and total vessel occlusion. The relevance of this paradigm to clinical triage and management is obvious and calls for testing in large clinical trials.

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