

Clinical Investigations

C-Reactive Protein as a Marker for Active Coronary Artery Disease in Patients with Chest Pain in the Emergency Room

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Summary

Background: Markers of inflammation, such as C-reactive protein (CRP), were found to be related to risk for cardiovascular disease (CVD) events in patients with angina pectoris. In addition, recent studies have shown that, in the case of atherosclerosis, increased CRP concentration reflects the inflammatory condition of the vascular wall.

Hypothesis: The study was undertaken to determine whether CRP levels in individuals with chest pain attending the emergency room (ER) may be used as a marker of active CVD.

Methods: Serum CRP level was measured in 226 of 326 consecutive patients (128 men, 98 women; mean age 61.3 ± 5.9 years; range 19–87 years) referred to the ER with chest pain. The decision whether to admit or release the subjects was determined without taking the CRP level into account. Follow-up was then performed for 1 year.

Results: Eighty-four patients were admitted to the hospital. Of these, 9 with acute coronary syndrome (ACS) had very high levels of CRP (25–40 mg/l), 35 had had an acute coronary event within the preceding 3 months, with levels of CRP 14–20 mg/l. Only eight patients with nonsignificant CVD had elevated CRP levels. Twenty-eight subjects who were released from the ER had elevated CRP levels (7–14 mg/l); 8 of these, in addition to 4 subjects with normal CRP levels, had a late coronary event.

Conclusion: This study indicates that in patients referred to the ER with chest pain and no other indication for hospitalization, a normal level of CRP suggests safe release. Most hospitalized patients with normal CRP will not have acute coronary syndrome. Patients who will develop early coronary events have very high CRP levels. High serum CRP level, after excluding other inflammatory sources, was proven to be a sensitive diagnostic and prognostic marker for significant coronary disease.

Key words: chest pain, cardiovascular disease, C-reactive protein, inflammation, atherosclerosis, emergency room

Introduction

Chest pain is considered to be the main complaint for which patients are usually referred to the emergency room (ER). Determining the cause of chest pain is one of the key tasks of physicians. Although it is one of the main manifestations of cardiac disease, it is crucial to recognize that the pain may originate from the heart or from a variety of another noncardiac intrathoracic structures. The clinical history, electrocardiogram (ECG), and levels of serum creatine phosphokinase (CPK) and troponin T/I still provide the most effective means for distinguishing an active coronary event from the many causes of chest pain, but their specificity and sensitivity are still far from ideal.¹

The clinical manifestation of acute coronary syndrome may largely depend on the presence and severity of functional factors that transiently and acutely interfere with coronary blood flow, together with an extremely variable degree of coronary atherosclerosis.²

Inflammation is an important feature of atheroma and is associated with activation and proliferation of macrophages, endothelial and smooth muscle cells, the generation of growth factors and cytokines, the presence of other proinflammatory mediators, and the activation and deposition of complement

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particles.³ Previous publications have also reported a powerful correlation between microbial infection, both within the arterial lesions themselves and elsewhere, and cardiovascular disease (CVD).⁴⁻⁶

A feature of most forms of inflammation, tissue damage, and infection is the increase in the circulating levels of various plasma proteins known as acute-phase reactant, such as C-reactive protein (CRP) and serum amyloid A protein (SAA). These reactants are mainly produced by hepatocytes through increased expression of their genes by cytokines, which are produced by activated macrophage. Sensitive assays for CRP and SAA have been developed.⁷ In healthy persons, CRP concentrations are very low, but they can rise tremendously in response to a wide variety of stimuli. The exact role of CRP remains unclear, but it can stimulate mononuclear cells to release tissue factor, which initiates coagulation, activates the complement pathway, and neutralizes platelet-activating factor.⁸

Earlier studies have examined CRP concentrations during the course of acute myocardial infarction.⁹ These studies were followed by several angiographic series and by cross-sectional and case-control studies, suggesting that CRP concentrations correlated directly with the presence and severity of coronary, cerebral, and peripheral arterial atherosclerosis.¹⁰⁻¹² In addition, various studies examined CRP concentrations among patients with angina pectoris. Liuzzo *et al.*¹³ reported that in patients admitted to the hospital with acute unstable angina, CRP levels above 3 mg/l were associated with a significantly worse prognosis. Furthermore, among patients with angina pectoris, increases in CRP concentrations were associated with unfavorable short- and long-term outcomes.¹⁴⁻¹⁷

In more recent years, several nested case-control and cohort studies have also reported that the risk for CVD was related to baseline CRP concentrations.^{18,19} This relation was interpreted as a confirmation of the role of CRP itself as a risk factor for coronary disease by inducing mononuclear cells to express tissue factor, the initiator of the extrinsic pathway of coagulation, further stimulating vascular thrombosis. In addition, increased CRP concentrations in atherosclerotic patients usually reflect the inflammatory condition of the vascular wall, which may play an important role of changes in plaque morphology, rupture, and thrombosis.^{20,21} We hypothesized that in patients referred to the ER with chest pain and no other sign of active coronary disease, and with normal CRP concentration, active coronary disease can be ruled out and the patients may be released from the ER.

Methods

Study Population

All patients who were referred to the ER between February and November 1999 because of typical or atypical chest pain were recruited for the study. Eligible patients for enrollment were women and men who had been referred to the ER because of typical or atypical chest pain, independent of the presence or absence of coronary risk factors. We excluded from the

study all individuals who were suspected to have a clinical situation that might induce high serum CRP concentration, such as acute or chronic coronary disease, cerebral vascular accident, peripheral vascular disease, intercurrent inflammatory or neoplastic conditions, surgery or major trauma in the last month, known thrombotic disorders, dilated cardiomyopathy, and valvular heart disease.

The Ethics Committee of the medical center approved this study, and all patients gave written informed consent.

Study Protocol

The decision to admit or release a patient from the ER was made by the attending physician according to the traditional considerations of symptoms, ECG, cardiac damage markers and enzymes, but blinded to the CRP serum levels. It was recommended that all participants perform a treadmill exercise test and undergo further coronary evaluation. The primary endpoints were the incidence of coronary events and/or cardiac death. After 1 year of follow-up, all suspected coronary events were reviewed by an independent endpoint committee according to standard diagnostic criteria. Sudden death from coronary causes was defined as death within 1 h of onset of cardiac symptoms.

C-Reactive Protein Assay

C-reactive protein was assayed using latex-enhanced nephelometry with a Behring Nephelometer Analyzer System and an NA Latex CRP Kit (Behring Diagnostics, Inc., Auckland, New Zealand).²² Quality control was carried out with daily runs of diluted standards prepared by Behring Diagnostics and standardized against the World Health Organization reference preparation of CRP serum. The range of values detected by the assay is 0 to 48 mg/l. With this method, the median normal value of CRP is 2–4.2 mg/l in 100% of normal healthy volunteers,²³ and conforms to a previous report using different methods.²⁴

Results

The level of CRP was defined in 40 healthy volunteers. The results are shown in Figure 1. All had normal serum CRP concentration.

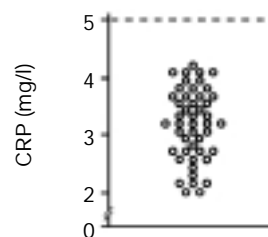


FIG. 1 C-reactive protein (CRP) levels in healthy subjects.

Of 326 consecutive patients who were referred to the ER for chest pain, 100 were excluded from this study because they were found to have variable clinical conditions that could provoke high serum CRP concentration. The remaining 226 patients (128 men, 98 women; mean age 61.3 ± 7 years; range 19–87 years) were recruited for the study. According to the Braunwald criteria for angina pectoris,¹ 84 patients were hospitalized (Group 1) and 142 (Group 2) were released following evaluation in the ER. Age, gender, cardiovascular risk factors, and baseline therapy were similar in both groups. All patients in both groups had normal ECG, and CPK, CPK-MB, and troponin T/I were within normal values. The characteristics of the patients are listed in Table I. High levels of serum CRP (5–45 mg/l) were found in 52 patients of Group 1, and coronary events occurred in 44 of these. In nine patients, the event occurred during hospitalization, mainly in those in whom CRP values were excessively high (> 25 mg/l), while in the remaining patients it occurred in the early weeks following hospitalization (Fig. 2). All had intermediate–high levels of CRP (14–20 mg/l). In 32 of the remaining 40 patients of Group 1, who had normal values of CRP, no coronary event occurred during the next year of follow-up, but some of them underwent exercise tests and/or thallium-image tests, and/or coronarography with nonsignificant CVD findings. No coronary event occurred in the remaining eight patients of this group during the next year of follow-up, although they had mild to moderately high levels of CRP (7–20 mg/l) (Fig. 2).

Of 142 patients in Group 2, 46 had withdrawn from follow-up, mainly because of personal reasons. Of the remaining 96 patients, 68 had normal levels of CRP (1–5 mg/l). Four of these, despite normal levels of CRP, were identified in the fourth trimester to have a coronary event. The remaining 28 patients in Group 2 were found to have moderately elevated levels of CRP (7–14 mg/l). Eight had coronary events in the second and third trimesters of follow-up while the remaining

20 patients had nonsignificant CVD (Fig. 2). High levels of CRP have a sensitivity of 93% and a specificity of 65% for acute coronary events, while normal CRP levels have a negative predictive value of 96%.

Discussion

Previous studies have registered elevated levels of CRP in patients with unstable angina pectoris and in those who have had a myocardial infarction, but these studies did not investigate its diagnostic importance.^{25, 26} The results of our study confirm the hypothesis that plasma concentration of CRP is elevated in the majority of patients who are referred to the ER with chest pain and develop myocardial infarction.

The syndrome of angina pectoris occurs most often in the setting of atherosclerotic coronary artery disease. Currently, it is generally believed that functional factors rather than size alone determine the propensity of atherosclerotic plaque for promoting active CVD. The most prominent and frequent clinical manifestation of this syndrome is chest pain, which constitutes an urgent challenge that needs immediate evaluation and clarification. Inflammations induce weakening of the fibrous cap of the atherosclerotic plaque, provoking its rupture, with subsequent exposure of the plaque core to blood components, resulting in formation of coronary thrombosis. A feature of most forms of tissue damage and inflammation is the increase in the circulating levels of CRP. In 1997, Haverkate *et al.* reported that raised circulating concentration of CRP might predict coronary events in patients with stable or unstable angina.¹⁴ More recently, Abdelmoutaleb *et al.*²⁷ demonstrated that increased CRP concentration, in case of atherosclerosis, reflects the inflammatory condition of the vascular wall.

TABLE 1 Characteristics of population

| Variables | Group 1 (n = 84) | Group 2 (n = 142) |
|----------------------|---------------------|----------------------|
| Age (years) (mean) | 60 ± 5 | 61 ± 8.2 |
| Sex (M/F) | 56/28 | 82/60 |
| Risk factors | | |
| Family history | 0 | 2 |
| Hypercholesterolemia | 0 | 4 |
| Diabetes | 9 | 13 |
| Hypertension | 21 | 25 |
| Smoking | 27 | 23 |
| Medication used | | |
| Nitrates | 0 | 0 |
| Beta blockers | 6 | 9 |
| Calcium blockers | 4 | 7 |
| Aspirin | 3 | 6 |
| ACE inhibitors | 19 | 16 |

Abbreviations: M = male, F = female.

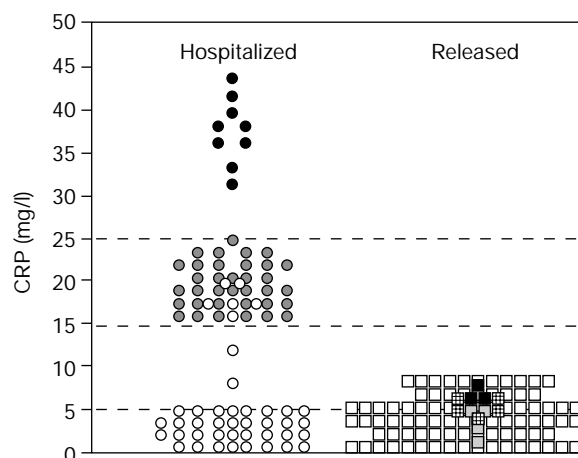


FIG. 2 C-reactive protein (CRP) levels in the hospitalized and released patients. ● = coronary syndrome (CS) during hospitalization, ● = CS during the first trimester, ■ = CS during the second trimester, ▣ = CS during the third trimester, □ = CS during the fourth trimester, ○ = nonsignificant coronary disease in hospitalized patients, □ = nonsignificant coronary disease in released patients.

The acute phase reactant CRP reflects an increased production of interleukin-1 and interleukin-6.^{28,29} The production of these two proinflammatory cytokines is triggered by most forms of underlying inflammation, tissue damage, and intercurrent infection.³⁰

The CRP response observed in patients who developed ACS may simply reflect the intrinsic inflammation conditions and tissue damage within the coronary vessel walls, which may contribute to both vasospasm and thrombosis. However, in addition it may reflect the central role of inflammation itself in the pathophysiology of active CVD. Several authors have suggested that CRP may directly interact with atherosclerotic vessels by activating the complement system, thereby promoting inflammation and thrombosis.³¹ Activated vascular wall cells, such as smooth muscle cells, endothelial cells, macrophages, and T lymphocytes, may play a central role because they produce interleukins, growth factors, procoagulant activity, and adhesion molecules that alter the vascular reactivity and thrombogenicity.^{32,33} Ridker *et al.*³⁴ have demonstrated that in apparently healthy men, high baseline plasma CRP level predicts the risk of future myocardial infarction, and that the use of aspirin, a well known anti-inflammatory drug, was associated with significant reduction in the risk of acute myocardial infarction.

Kuller *et al.*, in a nested case-control study of stored samples of serum from 492 controls and 246 coronary event cases in the Multiple Risk Factor Intervention Trial, found that a raised CRP concentration at entry was a highly significant risk factor,¹⁸ suggesting that CRP measurement may provide important prognostic information even before symptoms appear.

Our findings indicate that a normal level of CRP, in patients with chest pain referred to the ER, suggests not only a safe release but also negates early coronary syndrome. On the other hand, our findings suggest a close correlation between the level of CRP and the immediate risk for ACS. In practice, in the absence of any other intercurrent condition likely to provoke an acute phase response, the CRP assay may be sufficiently sensitive and precise to predict ACS. In healthy adults, the concentration of CRP is tightly regulated within the normal range. Large prospective studies are still necessary to confirm our findings.

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