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C-Reactive Protein
Increase in Unstable Coronary Disease
Cause or Effect?

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A crucial point in understanding the clinical and pathophysiologic meaning of C-reactive protein (CRP) elevation in acute coronary syndromes (ACS) is whether CRP release is predominantly a response to even small amounts of myocardial necrosis, for which troponin is a sensitive and specific marker, or is an independent indicator of the inflammatory process occurring in that clinical condition. Whereas troponin is a good predictor of both mortality and myocardial infarction (MI), although the highest values are associated with a decreased probability of MI, CRP predicts mortality but has no relation with the early or late occurrence of MI. The large variability of CRP values in ACS may depend on the different response of this inflammation marker to various stimuli, some patients being particularly hyperresponsive, especially those with elevated CRP values at baseline. We hypothesize that myocardial necrosis, as detected by troponin increases, would represent the strongest stimulus for CRP increase in ACS, causing in some patients, especially those with already-elevated CRP values at baseline, a disproportionate increase of this marker. Accordingly, the highest CRP values during ACS are likely to be observed in patients with already-elevated CRP values at baseline (which would increase the probability of having death and MI in the follow-up) and the highest troponin values (which would increase the probability of death in the follow-up, but not of subsequent MI). This hypothesis would explain why high CRP levels in unstable coronary disease are good predictors of death, but not of MI. (J Am Coll Cardiol 2005;46:1496–502) © 2005 by the American College of Cardiology Foundation

Acute coronary syndromes (ACS) result from coronary thrombosis occurring at sites of plaque rupture or superficial erosion (1–3). Plaques prone to rupture are characterized by a large lipid core, a thin fibrous cap, and an active inflammatory cell infiltrate, particularly located underneath disrupted portions of the cap, formed by monocyte-derived macrophages and by increased numbers of activated T lymphocytes and mast cells (4–6). These cells, once activated, produce proteolytic enzymes capable of degrading the collagen of the fibrous cap, halt collagen synthesis by smooth muscle cells, and regulate tissue factor production, representing the link between arterial inflammation and thrombosis (6).

Elevation of inflammatory markers is a common finding in non–ST-segment elevation ACS. Our group has reported some of the earliest observations on leukocyte function and inflammation in coronary artery disease (7–11), showing an increase of the leukocyte CD11b/CD18 receptor (a glycoprotein complex involved in the adhesion process of neutrophils and monocytes to endothelial cells) in the coronary sinus of patients with unstable angina, substantiating the hypothesis that an inflammatory component plays a role in the pathogenesis of this clinical manifestation (10–11). This observation stimulated further studies aimed at assessing the mechanism underlying the inflammatory outburst in such patients (12,13). Therefore we measured the expression of the CD11b/CD18 receptor, not only in the aorta and in the coronary sinus, but also in the post-obstructive chamber, immediately below the coronary narrowing identified as the culprit lesion (12). An increased expression of the CD11b/CD18 receptor was shown in the coronary sinus of these patients as compared with the aortic blood, whereas neutrophils and monocytes taken from the post-obstructive chamber showed an expression of the CD11b/CD18 receptor that did not differ from that shown by those leukocytes in the aortic blood. We concluded that activation of neutrophils and monocytes takes place at the microcirculatory interface with the injured myocardium, probably as a result of short but repeated episodes of myocardial ischemia. Using a similar approach, Cusack et al. (13) showed that interleukin (IL)-6 and tissue necrosis factor (TNF)-alpha levels were greater in the coronary sinus compared with the aortic root in unstable angina patients, suggesting intramyocardial production of these substances. Interestingly, the intracardiac gradient of these cytokines was found in patients with elevated troponin T levels, whereas it was no longer evident in those who were troponin negative. Moreover, in patients in whom blood samples had also been taken distal to the culprit coronary lesion, no differences were found in the levels of IL-6 and TNF-alpha between the
proximal and distal coronary artery despite the presence of a transcardiac cytokine gradient between the aortic root and the coronary sinus. These investigators concluded that the source of cytokine production lies within the myocardium and occurs in response to microinfarctions, as detected by increased troponin levels.

**C-REACTIVE PROTEIN AS A MARKER OF CORONARY INSTABILITY**

Among the various markers of inflammation proposed to monitor the clinical course of patients with non–ST-segment elevation ACS, C-reactive protein (CRP), an acute-phase reactant produced by hepatocytes in response to stimulation by inflammatory cytokines, primarily IL-6, is the most widely used. Although CRP levels may remain stable over long periods of time, they can increase several hundred-fold in response to inflammatory stimuli and are therefore useful in following up the disease activity in chronic conditions such as rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel diseases (14). Its use in unstable angina was proposed by Liuzzo et al. (15), who found that levels of CRP >3 mg/l on admission predicted a dire in-hospital outcome in 32 patients with that clinical condition.

Further observations underlined that CRP values undergo a dynamic process during hospitalization in such patients: Ferreiros et al. showed that (16), among 30 patients with values >3 mg/l on admission, values remained above that level in 12 patients, whereas they decreased in the remaining 18 patients. On the other hand, of 75 patients with CRP levels <3 mg/l on admission, elevated values developed in 30 patients, whereas in 45 patients values remained below the threshold of 3 mg/l (16). Discharge CRP values, and not admission values, were significantly related to the three-month outcome. Likewise, Biasucci et al. (17) found that elevated levels of CRP on discharge were significant predictors of recurrent instability in the next year.

The popularity of CRP as a marker of inflammation was further prompted by observations implicating CRP in vascular dysfunction and in the progression of atherosclerosis. Pasceri et al. (18) showed that incubation with recombinant human CRP induces a 10-fold increase in adhesion molecule expression in human endothelial cells, similar to that induced by activation with IL-1-beta, suggesting that such proinflammatory effects may contribute to the adverse outcome associated with higher levels of this acute-phase reactant. Moreover, CRP has been shown to attenuate the production of nitric oxide and prostacyclin by endothelial cells, supporting its role in the atherosclerotic process (19,20).

A crucial point in understanding the clinical and pathophysiologic meaning of CRP elevations in non–ST-segment elevation ACS is whether CRP release is predominantly a response to even small amounts of myocardial necrosis, for which troponin is a sensitive and specific marker, or is an independent indicator of the inflammatory process occurring in the coronary arteries in that clinical condition (21). The issue was addressed by Liuzzo et al. (22), who reported serial levels of CRP up to 96 h in 48 patients with unstable angina (all with troponin levels below 0.1 µg/l) and in 20 control patients with variant angina. On admission, the CRP level was significantly higher in unstable angina than in variant angina, although Holter monitoring showed a significantly greater total ischemic burden in the latter group of patients. However, ischemic episodes were longer in the unstable angina group than in the variant angina group. The temporal relation between changes in CRP and troponin was studied by Benamer et al. (23) in 195 patients with unstable angina. These investigators found a temporal link between early troponin I increases and later CRP elevations: in patients with increased troponin I on admission, CRP levels increased over the following 24 h, whereas in patients with normal troponin I on admission, CRP values remained unchanged. Likewise, using serial sampling, Cusack et al. (13) found that IL-6 and troponin concentrations increased in parallel over 48 h after hospital admission, suggesting a close relationship between systemic inflammatory activity and myocardial necrosis. The importance of serial sampling in unraveling the relationship between troponin and CRP is also underlined by Kennon et al. (24), who showed that CRP levels before discharge were correlated with troponin concentrations and predicted adverse outcome, whereas CRP levels drawn at admission (<6 h after symptom onset) were related to neither troponin concentration nor the occurrence of adverse events.

**PROGNOSTIC VALUE OF CRP AND ITS RELATIONSHIP TO TROPOinin CONCENTRATION**

The crucial issue, however, revolves around the prognostic role of CRP in non–ST-segment elevation ACS and its independence from troponin values. In their pioneering work, Liuzzo et al. (15) reported that CRP was a significant predictor of outcome unrelated to myocardial injury, because patients considered to be troponin-positive (that is, with values >0.2 µg/ml) were excluded from the study. Likewise, in the Thrombolysis In Myocardial Infarction (TIMI) 11B substudy, Morrow et al. (25) confirmed the short-term prognostic value of CRP in ACS; this inflammatory marker was related to the 14-day mortality rate, even in patients with a negative result on rapid troponin T assay,
which had a detection limit of 0.2 μg/l. These studies, however, cannot be considered sufficient proof of the independence of CRP from troponin values. In fact, a careful analysis of the FRagmin and Fast Revascularization during InStability in coronary artery disease (FRISC) II trial data (26) showed that even small amounts of released troponin T have important prognostic implications: the 1-year death rate was twice as high in patients with troponin values between 0.01 and 0.17 μg/l as compared with patients with concentrations <0.01 μg/l. Therefore, patients who were defined in earliest reports as “troponin negative” because they had values <0.2 μg/l might have had detectable concentrations of troponin T carrying important prognostic information. Another interesting finding of that analysis was the demonstration of a significant gradient of increasing risk of myocardial infarction (MI) up to concentrations of 0.63 μg/l, above which the risk of infarction dramatically decreased (26). Such a U-shaped relationship has been explained by the fact that patients with the highest troponin concentrations have already had a significant MI and are less likely to have unstable coronary lesions and sizable amounts of myocardium at risk (27).

Recent studies have attempted to unfold the complex relationship between CRP and troponin values in predicting the outcomes of patients with non–ST-segment elevation ACS. A major contribution was provided by the Global Utilization of Strategies to Open occluded arteries (GUSTO) IV study group, reporting the 30-day follow-up data in 7,108 patients with non–ST-segment elevation ACS (28). Figure 1 shows the relationship between values of troponin T and CRP values in that analysis. It is evident that patients with the largest increases of CRP values (those in the fourth quartile) had median troponin T concentrations that were three times as high as those observed in patients in the third CRP quartile. Although by multivariate analysis both increasing troponin T quartiles and increasing CRP quartiles gave an independent contribution to 30-day mortality, adjusted odds ratios (OR) were higher for troponin T (OR, 1.63; 95% confidence interval [CI], 1.43 to 1.87) than for CRP (OR, 1.19; 95% CI, 1.05 to 1.35). A surprising finding of that report was that, contrary to troponin, CRP values were not related to the 30-day MI rate. Figure 2, taken from the data presented in the GUSTO IV analysis (28), shows that at increasing levels of both CRP and troponin, the risk of mortality similarly increases, whereas the risk of MI increases at increasing troponin concentrations (although depicting the above-mentioned U-shaped relationship) but is not influenced by CRP levels. The superiority of troponin over CRP in assessing outcome in patients with non–ST-segment elevation ACS may account for the fact that troponin but not CRP is helpful in therapeutic triage of such patients by identifying those who will benefit from an invasive over a conservative strategy (29) or a particular antithrombotic treatment (30,31).

Other studies based on large populations have assessed the role of CRP in predicting short-term and long-term
outcome in non-ST-elevation ACS (32–36) (Table 1). In these studies, CRP levels were measured after the events qualifying for the inclusion (GUSTO IV trial, 9.5 h; C7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina [CAPTURE] trial, 8.7 h; FRISC trial, 5.5 h; Mueller et al. [35], not available) when the potential effects of myonecrosis on CRP levels were already present. The results of these studies are consistent in showing that CRP is able to predict mortality even though the highest odds ratios were observed for those studies that used a high cutoff level for troponin (0.10 μg/l). However, when death and MI were analyzed in combination, no significant relationship was found between CRP values and the combined end point. Only in the CAPTURE trial was CRP related to an increased cardiac risk represented by the combination of death and MI (34). However, the relative contribution of each variable to the final result is unknown because a separate analysis for mortality alone was not conducted. Moreover, troponin was dichotomized at the concentration of 0.10 μg/l and not analyzed as a continuous variable. All of these large studies consistently show that CRP levels do not predict the occurrence of MI in the follow-up of patients with non-ST-segment elevation ACS (37).

**Differential Implications of Troponin and CRP Increase in Non–ST-Segment Elevation ACS**

Figure 2 outlines the different prognostic significance of these two markers. Troponin is a good predictor of both mortality and MI, even though at the highest concentrations its ability to predict MI is lost. The highly significant gradient of increasing risk of mortality with increasing troponin levels is dependent on the progressive deterioration of left ventricular function with increasing troponin release (26,27). Moreover, positive troponin concentrations are associated with more visible thrombus and complex anatomy, reflecting the instability of coronary lesions and their propensity toward vessel occlusion, causing acute MI (38,39). On the other hand, CRP predicts mortality well, but has no relationship with the early or late occurrence of MI, making it very unlikely that the prominent CRP increases seen in patients with ACS would be in great part caused by the inflammatory process taking place in the coronary arteries, leading to plaque rupture or formation of coronary thrombi.

In this regard, it is interesting to analyze the variations observed in the CRP values one month after enrolment in recent ACS trials (40,41). Over that period of time, in the A to Z trial (40), CRP levels decreased similarly in the placebo group (from 20.4 to 2.5 mg/l) and in the group initially treated with 40 mg simvastatin (from 20.1 to 2.4 mg/l) despite a pronounced difference in low-density lipoprotein cholesterol (122 mg/dl in the placebo group and 68 mg/dl in the simvastatin group). Further decreases of CRP in the subsequent two-year follow-up period were more evident in the group taking 80 mg simvastatin than in the group taking 20 mg simvastatin and were associated with a lower cardiovascular mortality (4.1% vs. 5.4%). In the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT)-TIMI 22 trial (41), a lower-risk ACS population was enrolled an average of seven days after ACS: in this already-stabilized population, CRP levels at one month decreased more in the 80 mg atorvastatin group (from 12.3 to 1.3 mg/l) than in the 40 mg pravastatin group (from 12.3 to 2.1 mg/l) and were associated with a lower two-year coronary heart disease mortality (1.1% vs. 1.4%) (42). Taken together, these data show that the high values of CRP observed in ACS before clinical stabilization, as in the A to Z trial, decrease markedly (80% to 90% from their peak value) during the first month after the acute episode and are scarcely influenced, at least initially, by statin treatment. On the other hand, further decreases of CRP, over long stable phases of coronary disease, can be more frequently achieved using high doses of statins and have beneficial effects on cardiovascular events confirming that under stable clinical conditions CRP, as a key marker of inflammation, is an important determinant of cardiovascular risk. Indeed, among patients who achieved after one month of statin treatment low-density lipoprotein cholesterol levels of <70 mg/dl, those who had CRP levels >2 mg/l had a worse prognosis than patients who reached values below that threshold value (42). Another interesting finding of these large studies is the huge variability of CRP values in ACS patients. In the A to Z trial, the admission median values of CRP were 20.1 and 20.4 mg/l in the two study arms, with 25th and 75th percentile values ranging from 7.7 to 43.4 mg/l (40). Such a wide range of values may depend on the fact that CRP levels in ACS patients increase in response to various factors. As shown by Liuzzo et al. (43),
patients with unstable angina react differently to various stimuli, including coronary angiography and angioplasty. These investigators found a significant close correlation between the baseline levels of CRP and their increase after coronary angioplasty and coronary angiography, indicating that patients with already-elevated CRP values at baseline show hyperresponsiveness of this inflammation marker to these stimuli (43). Likewise, patients with acute MI preceded by pre-infarction angina who had higher admission CRP values than patients with unheralded MI also had higher peak CRP values during hospitalization, despite the fact that the necrotic insult, assessed by CK peak levels, was similar in the two groups of patients (44). Although the factors underlying the hyperresponsiveness of some patients with unstable angina are unknown, probably involving acquired and/or genetic mechanisms (45), it seems reasonable to conclude from the available data (43,44) that elevated baseline levels of CRP are markers of such hyperresponsiveness.

Figure 3 shows the possible relationship in ACS patients between their CRP values at baseline and the values achieved during ACS. The large variability of CRP values depends on the different response to various provocative stimuli, according to CRP baseline levels and to the intensity of the pro-inflammatory stimuli. We hypothesize that myonecrosis, as detected by troponin increases, would represent the strongest stimulus for CRP increase in ACS, resulting in some patients in a disproportionate increase of this marker. Accordingly, the highest CRP values during ACS are likely to be observed in patients with already-elevated CRP levels at baseline (which would increase the probability of having a new coronary event in the follow-up, including death and MI) and the highest troponin values (which would increase the probability of death in the follow-up, but not of subsequent MI). This hypothesis would explain why high CRP levels in unstable coronary disease are good predictors of death but not of MI. Further support for this hypothesis comes from the observation made by the European Concerted Action on Thrombosis and Disabilities (ECAT) Angina Pectoris Study, showing that elevated CRP levels highly correlate with low left ventricular ejection fraction (46). Surprisingly, no other studies have assessed the relationship between CRP levels and left ventricular function. A possible influence of decreased LV function on maintaining high CRP levels during stable phases of ischemic heart disease should also be considered, because circulating levels of proinflammatory cytokines are elevated in patients with heart failure (47).

An alternative explanation for the paradoxical finding of CRP being a predictor for death but not for MI is that CRP is able to predict only large, fatal MIs and not small, non-fatal MIs, particularly those defined primarily by cardiac biomarker elevations that are commonly associated with percutaneous revascularization procedures. Because the majority of MIs observed in the studies analyzed in Table 1, including the large GUSTO IV trial (28), were non-fatal, possibly related to interventional procedures, the relationship between CRP and MI might have been obscured. However, because elevated CRP levels have been shown to be sensitive predictors of adverse events, including MI, after percutaneous treatment (48,49) the methodology used to diagnose MI should have increased rather than decreased the ability of CRP to predict MI. It can also be speculated that elevated CRP values may favor the occurrence of fatal arrhythmias, but this intriguing hypothesis awaits confirmation by studies addressing the potential proarrhythmic effect induced by elevated CRP values (50).

CONCLUSIONS

It has been shown that CRP levels in the general population predict future cardiovascular events, including first-ever MI, stroke, and development of peripheral arterial disease (51); CRP may also provide a novel method of targeting statin therapy in both primary and secondary prevention of MI and stroke (52) as well as in the follow-up of stable patients after ACS (40–42). However, the levels of CRP in ACS are several-fold higher than those observed in the same patients in waning phases of their coronary disease (40–42). A large part of such huge increases is likely to reflect the inflammatory outburst secondary to the occurrence of myocardial necrosis, the highest values of CRP, which are associated with the highest short-term and long-term mortality, being found in patients with the largest increase in troponin concentrations. High CRP values are independent predictors of death in the follow-up of such patients, but are not associated with a greater risk of MI. These apparently contradictory findings may be explained by hypothesizing a strong influence of troponin values on CRP increase in ACS.
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