Clin. Cardiol. 25, 112–116 (2002)

Plasma C-Reactive Protein Predicts Left Ventricular Remodeling and Function after a First Acute Anterior Wall Myocardial Infarction Treated with Coronary Angioplasty: Comparison with Brain Natriuretic Peptide

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Summary

Background: C-reactive protein (CRP) directly participates in the myocardial injury of acute myocardial infarction (MI). Although high plasma CRP levels in the acute phase strongly indicate a poor early clinical outcome of patients with MI, the impact of CRP levels on late left ventricular (LV) function and remodeling, which are closely associated with long-term prognosis, remains unknown.

Hypothesis: Acute plasma CRP levels may predict late LV function and remodeling after MI.

Methods: We prospectively studied 12 consecutive patients with a first acute anterior MI recanalized by angioplasty. We measured plasma CRP levels on Days 0, 1, 2, 3, 4, and 7, and calculated the area under the curve (AUC). We also measured plasma brain natriuretic peptide (BNP) levels on Day 3 as the referential indicator of LV dysfunction and late LV remodeling. Late LV indices were independently assessed on a left ventriculogram obtained at 5.3 months to estimate the extent of LV remodeling.

Results: Plasma CRP reached its peak at Day 2.8 (8.68 ± 4.57 mg/dl). On linear regression analysis, the AUC of CRP (35.21 ± 19.33 mg/dl × day) correlated positively with BNP (316.5 ± 418.6 pg/ml) ($r = 0.646$, $p = 0.023$). The AUC of CRP, peak CRP, and BNP correlated significantly with late LV indices. Among these, the AUC of CRP showed the best correlation with end-diastolic volume index ($r = 0.765$, $p = 0.004$), end-systolic volume index ($r = 0.907$, $p < 0.001$), and ejection fraction ($r = -0.862$, $p < 0.001$).

Conclusions: Patients with high plasma CRP levels may be at risk for late LV dysfunction and remodeling; theoretically, their long-term prognosis may be poor. Measuring plasma CRP levels may provide valuable information for long-term risk stratification after MI.

Key words: acute myocardial infarction, brain natriuretic peptide, C-reactive protein, left ventricular remodeling

Introduction

Acute myocardial infarction (MI) triggers an acute phase response.[1] This response is induced by proinflammatory cytokines, which are released from the necrotic myocardium[2] and stimulate the liver to synthesize C-reactive protein (CRP).[3] The extent of CRP elevation in the peripheral blood is strongly associated with short-term postinfarct clinical outcome.[4–8]

Originally, CRP was regarded as only an indirect predictor reflecting the inflammation related to the extent of myocardial necrosis[4,5] or to the amount and activity of circulating proinflammatory cytokines such as interleukin-6.[2] However, CRP, especially human CRP, has drawn increasing attention since it was found to participate directly in local inflammatory reactions in the infarct myocardium through complement activation[9,10] that led to further tissue damage. Injection of human CRP into rats after ligation of the coronary artery enhances infarct size up to 40%.[9] On the other hand, complement depletion markedly reduces infarct size in the same model.[9] In humans, colocalization of CRP with activated C4 and C3 was found in specimens of infarct myocardium obtained between 12 h and 2 weeks after the onset of MI, but not in those of normal myocardium.[10] These observations imply that CRP is a major mediator of ischemic myocardial injury and may be a potent direct indicator of prognosis after MI. In this regard, it is widely accepted that high CRP levels indicate poor in-hospital

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Received: January 23, 2001
Accepted with revision: June 8, 2001

mortality and morbidity.[4–8] However, it has yet to be elucidated whether plasma CRP levels also predict long-term prognosis, especially in the era of reperfusion therapy.[11–13]

Left ventricular (LV) remodeling, which is mainly characterized by gradually progressing LV dilatation after MI, is strongly associated with long-term adverse cardiovascular events.[14–16] Provided that CRP is actively involved in the myocardial injury[9, 10] and CRP levels predict long-term cardiovascular events after MI, CRP levels may be associated with LV remodeling after MI. However, no study has yet addressed this point. Thus, in the present study, we investigated the link between acute plasma CRP levels and LV remodeling in the remote phase in patients with a first acute MI treated with angioplasty. We also measured plasma brain natriuretic peptide (BNP) levels as the referential serological indicator of LV dysfunction,[17, 18] long-term prognosis,[19–21] and LV remodeling after MI.[21–23]

Methods

Study Population

We prospectively studied 12 consecutive patients (10 men and 2 women; age, 66 ± 11 years) with acute MI who were admitted to the coronary care unit of Ogaki Municipal Hospital. Criteria for inclusion were (1) initial episode of MI, (2) a single culprit lesion in the proximal left anterior descending artery, (3) recanalization of the infarct-related artery with coronary angioplasty within 6 h of disease onset or between 6 and 24 h if evidence showed continuing ischemia, (4) receipt of patient's informed consent. Subjects excluded from the study were those with significant valvular disease or cardiomyopathy and those with concomitant diseases such as diabetes mellitus, virus liver disease, chronic renal failure, collagen disease, or infectious disease. The culprit lesions were segment 6 in four and segment 7 in eight patients. Killip class on arrival was class I in eight, class II in two, and class III in two patients. After angioplasty, all patients underwent adjunctive medical therapy following the standards of the coronary care unit.

Blood Sampling and Assays of Serological Parameters

Venous blood was sampled from all patients shortly after angioplasty on Days 1, 2, 3, 4, and 7. All samples were transferred immediately into chilled glass tubes containing ethylenediamine tetraacetic acid (1 mg/ml) and centrifuged at 4°C. Plasma samples were stored at −70°C and were later analyzed for BNP and CRP. Plasma BNP levels were determined in the samples obtained on Day 3 with a specific immunoradiometric assay kit of Shiono RIA BNP (Shionogi Co., Ltd., Osaka, Japan). The assay uses two monoclonal antibodies that recognize the carboxyterminal sequence and the ring structure of human BNP, respectively.[24] Plasma CRP levels of all samples were measured by immunoturbidimetric assay (N-assay TIA CRP-S; Nittobo Medical Co., Ltd., Tokyo, Japan) with the use of an autoanalyzer (Hitachi 7450, Hitachi, Ltd., Tokyo, Japan). The areas under the curve (AUC) of CRP, which were measured at points in time between immediately after angioplasty and Day 7, were also calculated because they are more closely associated with the true CRP release than the individual values.[5, 6] Serum creatine kinase levels were also measured upon the patient's admission and every 4 h after coronary angioplasty until the serum peak was identified.

Analysis of Left Ventriculogram

After the patients' discharge, they were seen every month at the outpatient clinic of Ogaki Municipal Hospital. Their medical treatment was determined individually by cardiologists in charge who were blinded to the results of the CRP and BNP assay. Follow-up coronary angiography and left ventriculography were performed at 5.3 ± 1.2 months. A single investigator who was completely blinded to the patients' clinical data analyzed the left ventriculograms obtained in the 30° right anterior oblique projection. Left ventricular volume was calculated by the Simpson's method for the analysis of end-diastolic volume index, end-systolic volume index, and ejection fraction in order to estimate LV remodeling.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation. Linear regression analysis was employed to assess the correlation between continuous variables. In this analysis, the log of plasma BNP levels was used to normalize the distribution data. A p value of < 0.05 was accepted as statistically significant.

Results

Serial Plasma C-Reactive Protein Levels and Clinical Course

The mean plasma CRP levels were 0.58 ± 1.23 mg/dl immediately after angioplasty. The levels reached their peak at 2.8 ± 0.6 days after disease onset and decreased thereafter. The mean peak CRP and AUC of CRP levels were 8.68 ± 4.57 mg/dl and 35.21 ± 19.33 mg/dl × day, respectively. During the follow-up period, the patient who showed the highest peak CRP level (16.5 mg/dl) and AUC of CRP (76.5 mg/dl × day) was rehospitalized because of congestive heart failure. None of the other patients had major cardiac events such as recurrent MI, congestive heart failure, or cardiac rupture.

Plasma Brain Natriuretic Peptide and Serum Peak Creatine Kinase Levels

Plasma BNP levels on Day 3 were higher than the upper normal limit (20.0 pg/ml) in all patients (316.5 ± 418.6 pg/ml). They correlated positively with the AUC of CRP ($r = 0.65$, $p = 0.023$) but not with peak CRP levels ($r = 0.46$, $p = 0.13$). Peak creatine kinase levels (4,000 ± 2,781 IU/l) did not correlate

with peak CRP levels ($r = -0.10$, $p = 0.75$), AUC of CRP ($r = -0.21$, $p = 0.52$), or BNP levels on Day 3 ($r = -0.36$, $p = 0.25$).

Relation between Serological Markers and Late Left Ventricular Indices

During the follow-up period, angiotensin-converting enzyme (ACE) inhibitors were given to 11 patients, aspirin was given to 11 patients, beta blockers were given to two patients. The levels of CRP and BNP of the patient who did not receive an ACE inhibitor were lower than the mean levels of the entire population. Patency of the infarct-related arteries was confirmed in all patients by follow-up coronary angiography. Figure 1 demonstrates the significant correlation between serological markers and LV indices. The AUC of CRP, peak CRP, and BNP on Day 3 correlated positively with late LV volume indices; they also correlated negatively with LV ejection fraction. Among them, the AUC of CRP showed the best correlation with LV indices. We found no correlation between peak creatine kinase levels and late LV indices (data not shown).

Discussion

The present study is the first to elucidate the significant link between plasma CRP levels and late LV indices in patients with a first anterior wall MI treated with angioplasty. To understand the link further, we also measured plasma BNP levels as a referential serological prognosticator of MI.

Acute MI provokes an acute phase response resulting in a rise of circulating CRP levels. The impact of CRP rise on the clinical outcome in the acute phase has been widely documented.[4–8] The magnitude of this rise correlates well with infarct size except when reperfusion therapy is given.[4, 5, 7] The peak value > 20 mg/dl indicates a high risk of cardiac rupture.[8] The reperfusion therapy reduces the rise in CRP, and this leads to a better outcome.[6, 7] The trend of CRP levels in the present study was similar to that of previous reports. The plasma CRP levels were within the normal limit or slightly elevated immediately after angioplasty and reached their peaks at Day 2.8.[4, 8] Neither peak CRP nor AUC of CRP were associated significantly with serum peak creatine kinase levels, which may reflect the effects of reperfusion.[6, 25]

It has not been fully elucidated whether CRP levels are long-term prognosticators after MI. Pietilä *et al.* reported that high serum CRP levels predict increased mortality up to 6 months after reperfusion therapy; the value of CRP in patients who died because of congestive heart failure or sudden cardiac death was higher than that in those who survived or died because of other causes.[11] However, CRP was no longer a predictor of mortality beyond 6 months after MI.[11] More recently, Tommasi *et al.* followed up patients with the first uncomplicated MI for a year and found that increased CRP levels detected

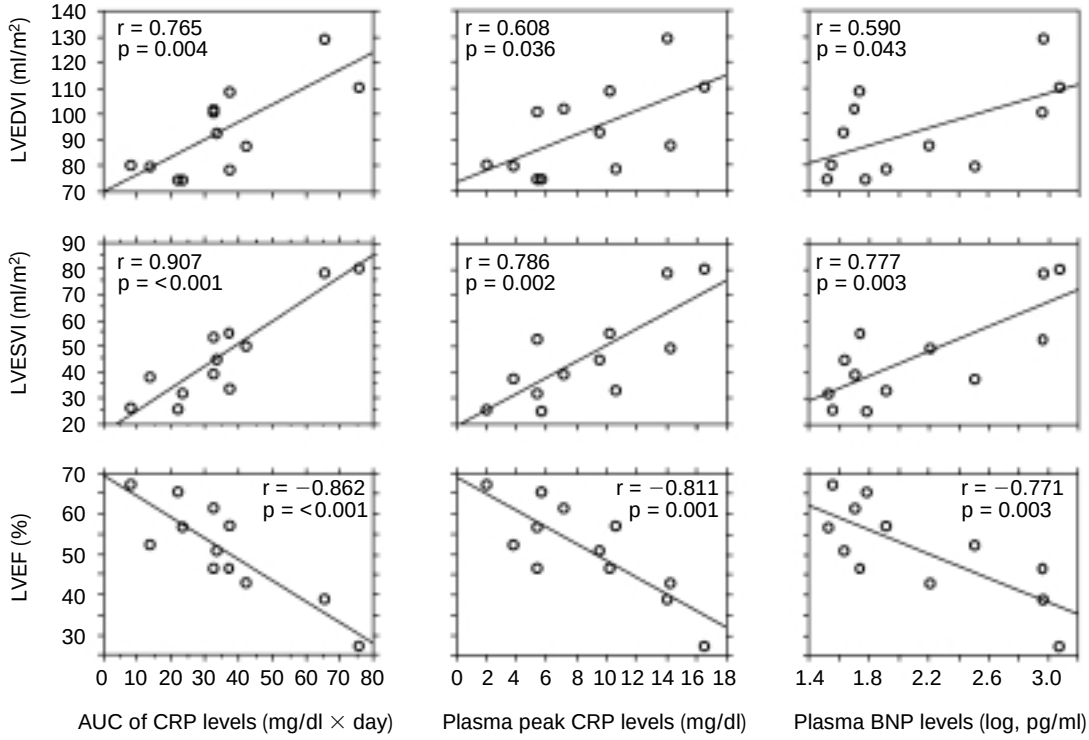

FIG. 1 Correlations of the area under the curve of plasma C-reactive protein (AUC of CRP) levels, the plasma peak C-reactive protein (CRP) levels, and plasma brain natriuretic peptide (BNP) levels with late left ventricular indices. Continuous lines are regression lines. LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index; LVEF = left ventricular ejection fraction.

8 h from disease onset were related to the incidence of subsequent cardiac events irrespective of other factors.[12] On the other hand, Nikfardjam *et al.* measured serum CRP levels in 729 patients with acute MI on admission and followed them for up to 3 years.[13] They found that those with elevated CRP levels were at an increased risk of dying; however, they contended that this association could largely be explained by other baseline variables including age, reperfusion therapy, and ischemic time. Although they studied a large number of subjects, their study had the following limitations. Because only half of the patients studied underwent reperfusion therapy, the results do not seem applicable in an era of reperfusion therapy. They measured CRP only on the patients' admission to the hospital. If they had included measurements of peak CRP in their study, the predictive value of CRP would have been more powerful.

Progressive LV dilatation after MI, an important feature of LV remodeling, is strongly associated with long-term adverse cardiovascular events.[14–16] In the management of patients who had survived the acute phase of MI, prevention of LV remodeling is crucial to reducing long-term morbidity and mortality.[15, 16] In the present study, both peak plasma CRP levels and the AUC of CRP correlated positively with LV volume indices at almost 6 months; that is, the higher the rise in circulating CRP, the more advanced the LV remodeling will be and the more it will lead to congestive heart failure and cardiac death. This is new evidence supporting the hypothesis that plasma CRP levels may predict a patient's long-term prognosis after MI.

Plasma BNP levels very sensitively reflect LV dysfunction in patients with acute MI.[17] Brain natriuretic peptide is released in increasing amounts throughout the ventricular myocardium, especially from the infarct zone, in patients with acute MI, presumably in response to increased regional wall stress.[18] It has also recently been established as a very sensitive prognosticator for risk stratification after MI. Elevated plasma BNP levels 3 days after MI indicates poor long-term prognosis for cardiovascular mortality independent of well-known predictors.[19, 20] More recently, the link between plasma BNP levels and LV remodeling has been elucidated in patients with acute MI. Nagaya *et al.* found that BNP predicts progressive ventricular remodeling at 1 month[22] and at 6 months[23] after MI. Richards *et al.* also reported that plasma BNP measured within 1–4 days of acute MI is a powerful independent predictor of LV function at 3–5 months and of heart failure and death over the subsequent 14 months.[21] Based on the above evidence, we measured plasma BNP levels on Day 3 as a referential indicator of LV dysfunction, long-term prognosis, and LV remodeling. In fact, plasma BNP levels on Day 3 correlated well with the LV indices in the remote phase, indicating that LV remodeling was prominent in patients who had high BNP levels.

In addition, there was a significant correlation between the AUC of CRP and BNP on Day 3. This implies that patients with highly elevated CRP suffer from severe LV dysfunction on Day 3, as shown by the increased BNP levels. Further, considering that BNP release reflects regional LV wall stress,[18] it should be noted that these patients also have increased regional LV wall stress, which is believed to cause LV remodeling.[14, 16] In fact, compared with plasma BNP levels, both plasma peak CRP levels and AUC of CRP correlated equally with late LV indices, or correlated even better than plasma BNP levels. These findings, based on plasma BNP as a reference, further support the hypothesis that plasma CRP levels may predict LV remodeling.

The limitations of this study need to be addressed. First, the number of the patients was small although the results of the present study are highly significant. Larger clinical studies are needed to confirm these observations. Second, medical treatments during the follow-up period were not completely the same among the patients. However, ACE inhibitor, the crucial agent for preventing LV remodeling,[26] was given to all patients except one whose CRP and BNP levels were lower than the mean levels of all patients. Thus, the bias raised by the differences in medical treatment may be neglected. Finally, the acute phase response may be enhanced in patients with preinfarction unstable angina compared with those with unheralded MI.[25] We did not address this point in the present study because we focused on the impact of plasma CRP elevation on the postinfarct LV function irrespective of preinfarction angina. It will be an interesting issue for future studies to elucidate how the differences in inflammatory response between patients with or without preinfarction angina affect their postinfarct clinical outcome.

Conclusion

Plasma CRP levels may be potent predictors of late LV function and remodeling after a first MI treated with angioplasty. Measuring CRP levels in the peripheral blood could provide valuable information for long-term risk stratification after MI.

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