C-Reactive Protein and Cardiac Troponin T in Risk Stratification: Differences in Optimal Timing of Tests Early after the Onset of Chest Pain

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Background: Increased C-reactive protein (CRP) is an important prognostic indicator for early risk stratification in patients with an acute coronary syndrome (ACS), independent of, and in combination with, increased cardiac troponin T (cTnT). However, increases in both cTnT and CRP also occur secondary to myocardial damage.

Methods and Results: In 156 consecutive patients, early release kinetics of CRP and cTnT were analyzed. The cutoff values were 3.0 mg/L for CRP and 0.1 μg/L for cTnT. In the 75 patients with a CRP below the cutoff on admission, there was little change in CRP until 8 h after the onset of symptoms. At 12 h after the onset of symptoms, the cumulative proportions of abnormal CRP and cTnT in non-ST elevation ACS patients were 27% and 89%, respectively (P < 0.01). During the first 24 h after the onset of symptoms, the median time above the cutoff was 20 h for CRP and 5 h for cTnT (P < 0.0001). CRP was below the cutoff on admission significantly more often among patients receiving thrombolytic therapy than in patients without an indication for reperfusion therapy (51% vs 28%; P = 0.004).

Conclusions: Increased CRP as an early independent risk indicator should be measured as soon as possible after the onset of symptoms, whereas increased cTnT is most reliable at 12 or more hours after the onset of symptoms.

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Several studies have indicated that small differences in baseline concentrations of C-reactive protein (CRP) in apparently healthy men and in patients with stable angina pectoris constitute an independent risk for first cardiovascular events (1–4). In addition, the increase in CRP after acute myocardial infarction (AMI) and CRP concentrations during unstable angina and at discharge correlate with the risk of a recurrent event (5–10). Recently, it has been shown in patients with unstable angina that increased CRP is associated with adverse outcome independent of an increased cardiac troponin T or I (cTnT and cTnI), which are sensitive and specific markers of myocardial necrosis and strong prognostic indicators (11–13). For CRP to be associated with outcome independently from troponin, the pathophysiological process causing increases in CRP or cTnT is expected to be different. Increases in CRP in these patients are hypothesized to be the result of inflammatory activation, infectious or otherwise, irrespective of the presence or absence of myocardial necrosis. AMI itself induces an acute phase inflammatory reaction that is characterized by an increase in CRP (14–16). Peak CRP concentrations correlate with infarct size (6, 7), although this correlation is less significant after successful early reperfusion therapy (7). Moreover, it was demonstrated that increases in CRP do not occur after episodes of myocardial ischemia without necrosis in patients with variant angina (17). Therefore, for CRP to have early prognostic significance independent of markers of myocardial necrosis, such as cardiac troponin in patients with an acute coronary syndrome (ACS), blood samples should be taken before CRP becomes increased as a result of myocardial damage alone. The aim of the
present study was to characterize the early increase in CRP as a consequence of myocardial damage and compare this to the early rise in cTnT. From these data, the optimal timing for early cTnT and CRP sampling for prognostic purposes is proposed.

**Materials and Methods**

Consecutive patients admitted to the Cardiac Emergency Department of the Academic Medical Center were included in the study. Blood samples were drawn with an indwelling intravenous catheter at 3, 4, 5, 6, 7, 8, 12, 16, 20, and 24 h after the onset of symptoms. Patients were eligible for the study when there was typical chest pain suggestive of myocardial ischemia within the previous 12 h before admission and evidence of myocardial damage, indicated by at least one blood sample within the first 24 h with a cTnT >0.1 μg/L. Exclusion criteria were severe skeletal muscle damage or trauma, cardiac resuscitation, infectious disease or signs of inflammation, and inability or refusal to give informed consent.

Patients with ST elevation or new left bundle branch block on the admission electrocardiogram (ECG) were treated with thrombolytics; other patients were treated with aspirin, intravenous unfractionated heparin, intravenous nitrates, and β-blockers at the discretion of the attending physician.

CRP and cTnT were measured batchwise. Results for creatine kinase MB isoenzyme (CK-MB; EC 2.7.3.2) were made available, but the physicians were unaware of CRP and cTnT results.

The protocol was approved by the institutional review board, and all patients gave informed consent.

Blood was collected in 10-mL heparin-coated tubes and centrifuged without delay. Cells were discarded, and plasma was stored at −20 °C until further analysis.

CK-MB mass was measured immunochemically (ACS: 180 analyzer; Bayer) (18). The upper reference limit was 7.5 μg/L, and the assay was linear from 0 to 500 μg/L. Troponin T was measured by ELISA on an ES300 analyzer (Boehringer Mannheim) (19). The upper reference limit was 0.1 μg/L, and the assay was linear from 0 to 15 μg/L. CRP was measured with a nephelometric assay (Behring Diagnostics) (20). The detection limit was 0.2 mg/L, the assay was linear from 0.2 to 230 mg/L, and the CV was <3% at a concentration of 2 mg/L. For the present analysis, we used a cutoff value of 3.0 mg/L, as reported previously (10, 17, 21). All calibrators were supplied by the manufacturers.

Patients were divided into two groups: group 1, which included patients with a CRP >3.0 mg/L on admission; and group 2, which included patients with CRP >3.0 mg/L on admission. The median values and interquartile ranges for CRP and cTnT were plotted for each time point. We calculated the cumulative proportion of patients with an abnormal CRP and cTnT over the first 24 h after the onset of symptoms.

The time points at which CRP and cTnT exceeded the cutoff values were recorded for each patient. The interval between these time points was compared in groups 1 and

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**Table 1.** Consecutive patients with chest pain who had an abnormal cTnT (>0.1 μg/L) during the first 24 h after the onset of symptoms.

<table>
<thead>
<tr>
<th>Group 1 (CRP ≤3.0 mg/L; n = 75)</th>
<th>Group 2 (CRP &gt;3.0 mg/L; n = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), years</td>
<td>59 (35–90)</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>51 (68%)</td>
</tr>
<tr>
<td>Previous AMI, n (%)</td>
<td>17 (23%)</td>
</tr>
<tr>
<td>Previous PTCA, n (%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Previous CABG, n (%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Thrombolytics, n (%)</td>
<td>35 (51%)</td>
</tr>
<tr>
<td>CRP adm, mg/L</td>
<td>1.55 (0.6–2.0)</td>
</tr>
<tr>
<td>cTnT adm, μg/L</td>
<td>0.03 (0.01–0.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 2 (CRP &gt;3.0 mg/L; n = 81)</th>
<th>Group 2 (CRP &gt;3.0 mg/L; n = 81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), years</td>
<td>67 (36–88)</td>
</tr>
<tr>
<td>Males, n (%)</td>
<td>57 (70%)</td>
</tr>
<tr>
<td>Previous AMI, n (%)</td>
<td>21 (26%)</td>
</tr>
<tr>
<td>Previous PTCA, n (%)</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>Previous CABG, n (%)</td>
<td>12 (15%)</td>
</tr>
<tr>
<td>Thrombolytics, n (%)</td>
<td>23 (28%)</td>
</tr>
<tr>
<td>CRP adm, mg/L</td>
<td>7.3 (5.2–13.0)</td>
</tr>
<tr>
<td>cTnT adm, μg/L</td>
<td>0.11 (0.03–0.2)</td>
</tr>
</tbody>
</table>

* Patients were divided in two groups according to their admission CRP status: CRP ≤3.0 mg/L (group 1) and CRP >3.0 mg/L (group 2).

a–d Significantly different from group 1: a P <0.0001; c P = 0.004; d P = 0.015.

a CABG, coronary artery bypass graft.

f Values for CRP and cTnT on admission are given as median and 25th and 75th percentiles.
2, using the generalized Wilcoxon signed-rank test, and median difference and interquartile range were calculated. The proportions of patients that were treated with thrombolytics in groups 1 and 2 were compared with the \( \chi^2 \) test. \( P < 0.05 \) was considered statistically significant.

**Results**

A total of 156 patients were included in the study. Baseline characteristics of the patients are given in Table 1. Histories of previous AMI, percutaneous transluminal coronary angioplasty (PTCA), or coronary artery bypass graft were equally present in both groups. Eighty-nine percent of patients presented within 6 h of the onset of symptoms. Sixty-one patients with ST elevation received thrombolytic therapy. Median CRP on admission was 1.55 mg/L in group 1 and 7.3 mg/L in group 2. Patients with increased CRP on admission were older. Patients in group 1 were significantly more likely to have ST elevation on the admission ECG and to receive thrombolytic therapy than group 2. Median cTnT on admission was significantly higher in group 2.

Median CRP in both groups 1 and 2 changed little until 8 h after the onset of symptoms (Fig. 1). The median CRP and cTnT values and 25th and 75th percentiles for each time point for the patients in group 1 are shown in Fig. 2, with results for the 38 patients treated with thrombolytic therapy (Fig. 2A) shown separately from those for the other 37 patients (Fig. 2B). Although the increases in CRP and cTnT were less profound in the patients not treated with thrombolytic therapy, the patterns were similar, with an early increase in cTnT and a time lag of several hours before CRP began to increase. The cumulative proportion of patients with a sample above the cutoff value for CRP and cTnT over time are shown in Fig. 3. In the patients who received thrombolytics (Fig. 3A), at 5 and 6 h after the onset of symptoms, 68% and 84% of patients had an abnormal cTnT concentration, whereas only 8% and 18% of patients had an abnormal CRP concentration (\( P < 0.01 \)). For patients not receiving thrombolytics (Fig. 3B), at 5 and 6 h, 46% and 62% had an abnormal cTnT concentration, and 5% and 11% had an abnormal CRP concentration (\( P < 0.01 \)). At 12 h, the cumulative proportions of abnormal CRP and cTnT concentrations in non-ST elevation ACS patients were 27% and 89%, respectively (\( P < 0.01 \)). Median time above the cutoff value was 20 h for CRP (interquartile range, 12 to >24 h) and 5 h for cTnT.
The median time interval between increases in CRP and cTnT above their cutoff values was 9 h (interquartile range, 3–18 h). The potential correlation between admission CRP and cTnT in the lower concentration ranges was analyzed, and the results are plotted in Fig. 4, with the patients who received thrombolytics plotted separately from the other patients. Although patients receiving thrombolytic therapy had a CRP below the cutoff value of 3.0 mg/L more frequently than patients who did not receive thrombolytics, a substantial increase in CRP on admission did occur in some patients receiving thrombolytics.

**Discussion**

This is the first study demonstrating the differences in early release kinetics of plasma CRP and cTnT in patients with an ACS, using hourly sampling, carefully timed relative to the onset of symptoms. CRP is synthesized in the liver as part of the acute phase response stimulated by the pro-inflammatory cytokine interleukin-6 (22). It was shown by Neumann et al. (23) in patients undergoing primary PTCA for AMI that interleukin-6 is released from the myocardium and can be detected in the coronary sinus within minutes after reperfusion of the infarct-related artery. For plasma CRP to become increased, therefore, some time lag is to be expected: cytokine release as a result of tissue damage precedes synthesis and subsequent increases in CRP in plasma after the onset of myocardial damage. This is in contrast to cTnT release, which occurs from the cytosolic cTnT pool from injured cardiac myocytes directly into the interstitium and the plasma (24). In 1978, Kushner et al. (25) reported on CRP kinetics after AMI. These authors noted a lag period of up to 22 h for the increase in CRP to occur in some but not all patients. Pietilä et al. (16) reported on increases in CRP over time in 10 patients with AMI documented with CK and CK-MB. Using a reference interval of 0–10 mg/L for CRP and frequent blood sampling, they found that 7 of 10 patients had an increased CRP “which began to increase 24 h (SD 9) after onset of symptoms and peaked after 83 (SD 30) hours”. These authors already noted that, whereas on average CRP was correlated with infarct size and...
In contrast, in the study by Liuzzo et al. from the relationship between the CRP and cTnT values, increased risk factor for the combined endpoint in this study. In multivariate analysis, increased CRP was not an independent to time of symptoms, and cardiac troponins were not measured. We have reported previously that increases in CRP may be the result of myocardial necrosis, which is already represented by an increase in troponin.

Careful timing of CRP and cTnT sampling relative to the onset of symptoms has not been performed routinely in most studies, and this may have implications for the interpretation of the results. The predictive power of CRP independent of cTnT may be increased with carefully timed sampling. In the study by Haverkate et al. (28) on the prognostic value of CRP in patients with stable and unstable angina, blood sampling was not performed relative to time of symptoms, and cardiac troponins were not measured. Toss et al. (29) reported on the prognostic value of CRP in a substudy of FRISC-1. Blood samples “were collected at inclusion”, and the authors noted that both fibrinogen and CRP concentrations were higher in patients with increased troponin compared with patients with a troponin concentration below the cutoff. In a multivariate analysis, increased CRP was not an independent risk factor for the combined endpoint in this study. This may have been attributable to the timing of blood sampling, which thus included patients with increased CRP solely as a result of myocardial damage, as is evident from the relationship between the CRP and cTnT values.

In contrast, in the study by Liuzzo et al. (8), which demonstrated that an abnormal CRP concentration is a strong prognostic indicator, blood samples were taken on admission, patients with unstable angina pectoris had symptoms within the last 48 h, and all had troponin T concentrations below the cutoff. In addition, Rebuzzi et al. (9) found a strong relationship between CRP and adverse cardiac events independent of cTnT in patients with severe unstable angina pectoris. In this study, blood samples were taken on admission, which occurred a mean of 11 h after the last anginal episode. Morrow et al. (12) showed in a substudy of TIMI 11A that a CRP >15.5 mg/L was associated with 14-day mortality in combination with increased troponin T. In the 91 patients with an abnormal rapid bedside cTnT test, those with increased CRP had a 5.1% mortality rate, whereas in patients with a normal CRP there was no mortality. In that study, samples were drawn on enrollment, at least 6 h after the onset of symptoms. A recent report by Ferreiro et al. (30) demonstrated a strong relationship between CRP on admission and adverse cardiac events in patients with unstable angina. Admission samples were taken a median of 12 h after the onset of symptoms, but troponin T was not measured. We have reported previously that the incidence of combined cardiac death, nonfatal AMI, or admission for recurrent unstable angina was 42% in patients with increased CRP and cTnT, 4.5% in patients with increased cTnI and normal CRP, and 11% in patients with an abnormal CRP and a normal cTnI. Blood samples were taken on admission in patients admitted within 8 h after the onset of symptoms, when increases in CRP attributable to myocardial necrosis are not yet expected (13).

A substantial proportion of patients in our present study with evidence of myocardial damage (an increase in cTnT within the first 24 h) had an abnormal CRP and a cTnT below the cutoff on admission. A recent report by Liuzzo et al. (21) that showed that CRP concentrations on admission were normal more often in patients with unheralded myocardial infarction than in patients with preinfarction angina. Patients with unheralded myocardial infarction more often show ST elevation on the admission ECG, necessitating reperfusion therapy. Our data show that in patients with ST-elevation myocardial infarctions requiring reperfusion therapy, there is no correlation between admission CRP and cTnT concentrations, in either the higher or the lower concentration ranges. Therefore, our data do not substantiate that “unheralded myocardial infarction and unstable angina may be related to different pathogenic components” as suggested by Liuzzo et al. (21), but they do suggest that these relationships are complex.

Our data are in accordance with results from the GUSTO-IIa study, which indicated that in a substantial proportion of patients, cTnT increased 8 and 16 h after the baseline cTnT measurement (31). An early invasive treatment strategy was recently shown to be beneficial in high-risk patients identified by increased cTnT (32), and in the MITI registry there was a significantly lower long-term mortality in patients admitted to hospitals favoring a very early (≤6 h) invasive strategy (33). In the
light of these findings, an increased cTnT measured early after admission may direct early treatment decisions, keeping in mind that patients with a cTnT below the cutoff on admission may show an increase in troponin T during subsequent hours.

This study has several limitations. Blood samples were taken relative to the time of onset of symptoms. In patients with a non-ST elevation ACS, time of onset of symptoms may be uncertain. In addition, in this relatively small patient group, we focused on plasma kinetics of the markers, and we cannot relate our findings to the clinical follow-up of these patients. Finally, a careful history of preinfarction angina was not routinely recorded on admission, and we are not able to reliably distinguish between patients with “un heralded” or “heralded” myocardial infarctions.

Our data indicate that for increases in CRP to be an independent prognostic indicator in patients with an increased cTnT, only a short time window exists after the onset of myocardial damage during which baseline CRP concentrations can be measured in most patients. In the majority of patients with baseline CRP values below the cutoff on admission, a increase in CRP at a later time point could be caused by an inflammatory reaction that is initiated by myocardial necrosis. Thus, for early risk stratification, blood samples for CRP measurements are preferably taken as soon as possible after the onset of symptoms, if possible within 8 h. In contrast, increased cTnT is most reliably measured from 12 h after the onset of symptoms. In that way, CRP measurements could be used in combination with cTnT measurements as part of a clinical decision protocol for early risk stratification and subsequent treatment (e.g., glycoprotein IIb/IIIa inhibitor treatment and early percutaneous intervention) (34), especially in patients with a non-ST elevation ACS.

References


