Early risk stratification in patients with chest pain
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Chapter 9

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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ABSTRACT

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

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

Conclusion
An increased C-reactive protein as an early independent risk indicator should be measured as soon as possible after the onset of symptoms, whereas increased troponin T is most reliably measured at 12 or more hours after the onset of symptoms.
INTRODUCTION

Several studies have indicated that small differences in baseline concentrations of C-reactive protein in apparently healthy men and in patients with stable angina pectoris constitute an independent risk for first cardiovascular events(129;130;193;194). In addition, both the increase in C-reactive protein after acute myocardial infarction and C-reactive protein concentrations during unstable angina and at discharge correlate with the risk of a recurrent event. (124;128;195-198)Recently, it has been shown in patients with unstable angina that increased C-reactive protein is associated with adverse outcome independent of an increased cardiac troponin T or I, which are sensitive and specific markers of myocardial necrosis and strong prognostic indicators(12;13;199). For C-reactive protein to be associated with outcome independently from troponin, the pathophysiological process causing increases in C-reactive protein or troponin T is expected to be different. Increases in C-reactive protein in these patients are hypothesized to be the result of inflammatory activation, infectious or otherwise, irrespective of the presence or absence of myocardial necrosis. Acute myocardial infarction itself induces an acute-phase inflammatory reaction that is characterized by an increase in C-reactive protein(200-202). Peak C-reactive protein concentrations correlate with infarct size(196;197), although this correlation is less significant after successful early reperfusion therapy(197). Moreover, it was demonstrated that increases in C-reactive protein do not occur after episodes of myocardial ischemia without necrosis in patients with variant angina(183). Therefore, for C-reactive protein to have early prognostic significance independent of markers of myocardial necrosis such as cardiac troponin in patients with an acute coronary syndrome, blood samples should be taken before C-reactive protein becomes increased as a result of myocardial damage alone. The aim of the present study was to characterize the early increase in C-reactive protein as a consequence of myocardial damage and compare this to the early rise in cardiac troponin T. From these data, the optimal timing for early troponin T and C-reactive protein sampling for prognostic purposes is proposed.
MATERIALS AND METHODS

Consecutive patients admitted to 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 hours 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 hours before admission and evidence of myocardial damage indicated by at least one blood sample within the first 24 hours with a troponin T > 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 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.

C-reactive protein and troponin T were measured batchwise. Creatine kinase-MB isoenzyme were made available, but the physicians were unaware of C-reactive protein and troponin T 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.

Creatine kinase-MBmass was measured immunochemically (ACS:180 analyzer, Bayer)(203). 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)(204). The upper reference limit was 0.1 μg/L, and the assay was linear from 0-15 μg/L. C-reactive protein was measured with a nephelometric assay (Behring Diagnostics, Marburg, Germany)(205). The detection limit was 0.2 mg/L, the assay was linear from 0.2-230 mg/L, and the coefficient of variation 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(128;183;206). All calibrators were supplied by the manufacturers.

Patients were divided into two groups: group 1, which included patients with a C-reactive protein ≤3.0 mg/L on admission; and group 2, which included patients with C-reactive
protein > 3.0 mg/L on admission. The median values and interquartile range for C-reactive protein and troponin T were plotted for each time point. We calculated the cumulative proportion of patients with an abnormal C-reactive protein and troponin T over the first 24 hours after symptoms onset.

The time points at which C-reactive protein and troponin T exceeded the cutoff values were recorded for each patient. The interval between these time points was compared in group 1 and 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 group 1 and 2 were compared with the chi-square test. A p-value of <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 acute myocardial infarction, percutaneous transluminal coronary angioplasty or coronary artery bypass grafting were equally present in both groups. Eighty-nine percent of patients presented within 6 hours of the onset of symptoms. Sixty-one patients with ST-elevation received thrombolytic therapy. Median C-reactive protein on admission was 1.55 mg/L in group 1, and 7.3 mg/L in group 2. Patients with increased C-reactive protein on admission were older. Patients in group 1 were significantly more likely to have ST-elevation on the admission electrocardiogram and to receive thrombolytic therapy than group 2. Median troponin T on admission was significantly higher in group 2. Median C-reactive protein levels in both groups 1 and 2 changed little until 8 hours after the onset of symptoms (figure 1). The median C-reactive protein and troponin T values and 25th and 75th percentiles for each time point for the patients in group 1 are shown in figure 2, with results for the 38 patients treated with thrombolytic therapy (figure 2A) shown separately from those for the other 37 patients (figure 2B). Although the increases in C-reactive protein and troponin T were less profound in the patients not treated with thrombolytic therapy, the patterns were similar, with an early increase in troponin T and a time lag of several hours before C-reactive protein began to increase. The cumulative proportion of patients with a sample above the cut-off value for C-reactive protein and troponin T over time are shown in figure 3. In the patients who received
Optimal timing

thrombolytics (figure 3A), at 5 and 6 hours after the onset of symptoms, 68% and 84% of patients had an abnormal troponin T, whereas only 8% and 18% of patients had an abnormal C-reactive protein concentration (p<0.01). For patients not receiving thrombolytics (figure 3B), at 5 and 6 hours, 46% and 62% had an abnormal troponin T, and 5% and 11% had an abnormal C-reactive protein (p<0.01). At 12 hours, cumulative proportions of abnormal C-reactive protein and troponin T in non-ST-elevation ACS patients were 27% and 89%, respectively (p<0.01). Median time above the cutoff value was 20 hours for C-reactive protein (interquartile range 12 to >24 hours) and 5 hours for troponin T (interquartile range 4-7 hours; Wilcoxon signed rank test Z=7.014, p<0.0001). The median time interval between increases in C-reactive protein and troponin T above their cutoff values was 9 hours (interquartile range 3-18 hours). The potential correlation between admission C-reactive protein and troponin T in the lower concentration ranges was analyzed, and the results are plotted in figure 4, with the patients who received thrombolytics plotted separately from the other patients. Although patients receiving thrombolytic therapy had a C-reactive protein below the cutoff value of 3.0 mg/L more frequently than patients who did not receive thrombolytics, a substantial increase in C-reactive protein on admission did occur in some patients receiving thrombolytics.

DISCUSSION

This is the first study demonstrating the differences in early release kinetics of plasma C-reactive protein and troponin T in patients with an acute coronary syndrome using hourly sampling, carefully timed relative to the onset of symptoms. C-reactive protein is synthesized in the liver as part of the acute phase response stimulated by the pro-inflammatory cytokine interleukin-6(207). It was shown by Neumann et al.(208) in patients undergoing primary percutaneous transluminal coronary angioplasty for acute myocardial infarction that IL-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 C-reactive protein 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 C-reactive protein in plasma after the onset of myocardial damage. This is in contrast to troponin T release, which occurs from the cytosolic troponin T pool from injured cardiac myocytes directly into the interstitium and the plasma(209). In 1978, Kushner et al.(210) reported on C-reactive protein kinetics after acute
myocardial infarction. These authors noted a lag period of up to 22 hours for the increase in C-reactive protein to occur in some, but not all patients. Pietilä et al. (202) reported on increases in C-reactive protein over time in 10 patients with acute myocardial infarction documented with creatine kinase and creatine kinase-MB. Using a reference interval of 0-10 mg/L for C-reactive protein and frequent blood sampling, they found 7 of 10 patients had an increased C-reactive protein “which began to increase 24 hours (SD 9) after onset of symptoms and peaked after 83 (SD 30) hours”. These authors already noted that, whereas on the average C-reactive protein was correlated with infarct size and increases in CK, some patients had small infarcts and a substantial increase in C-reactive protein.

In the present study, we used a sensitive C-reactive protein assay with better precision in the lower concentrations range, a cutoff value of 3.0 mg/L, and hourly blood sampling until 8 hours after the onset of symptoms and at 4 hours intervals until 24 hours. We demonstrated that in patients with myocardial necrosis documented by an increase in troponin T, C-reactive protein values start to increase as a consequence of myocardial necrosis at a later time than troponin T. In patients with a normal C-reactive protein concentration below the cutoff on admission who did not show ST-elevation on the admission ECG, at 5 hours after the onset of symptoms, C-reactive protein values were 3.0 mg/L in only 5.4% of patients, whereas nearly 50% have an abnormal troponin T. At 8 hours, 16% of patients had an abnormal C-reactive protein, and 76% had an abnormal troponin T. This implies that for C-reactive protein to have prognostic value independent of troponin T, samples should be taken as early as possible after the onset of symptoms, whereas an increase in troponin T is detected most reliably from 12 hours after the onset of symptoms (29;41;44). Otherwise, increases in C-reactive protein may be the result of myocardial necrosis, which is already represented by an increase in troponin.

Careful timing of C-reactive protein and troponin T 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. Predictive power of C-reactive protein independent of troponin T may be increased with carefully timed sampling. In the study by Haverkate et al. (184) on the prognostic value of C-reactive protein 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. (127) reported on the prognostic value of C-reactive protein in a substudy of FRISC-1. Blood samples “were collected at inclusion” and the authors noted that both fibrinogen and C-reactive protein concentrations were higher in
patients with increased troponin compared with patients with a troponin concentration below the cutoff. In a multivariate analysis, increased C-reactive protein 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 C-reactive protein solely as a result of myocardial damage, as is evident from the relationship between the C-reactive protein and troponin T values. In contrast, in the study by Liuzzo et al. (124) which demonstrated that an abnormal C-reactive protein concentration is a strong prognostic indicator, blood samples were taken on admission, patients with unstable angina pectoris had symptoms within the last 48 hours, and all had troponin T concentrations below the cutoff. In addition, Rebuzzi et al. (198) found a strong relationship between C-reactive protein and adverse cardiac events independent of troponin T in patients with severe unstable angina pectoris. In this study, blood samples were taken on admission, which occurred a mean of 11 hours after the last anginal episode. Morrow et al. (13) showed in a substudy of the TIMI 11A that a C-reactive protein above 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 troponin T test, those with an elevated C-reactive protein had a 5.1% mortality rate, whereas in patients with a normal C-reactive protein there was no mortality. In that study, samples were drawn on enrollment, at least 6 hours after the onset of symptoms. A recent report by Ferreirós et al. (211) demonstrated a strong relationship between C-reactive protein on admission and adverse cardiac events in patients with unstable angina. Admission samples were taken a median of 12 hours after the onset of symptoms, but troponin T was not measured. We have reported previously that the incidence of combined cardiac death, non-fatal acute myocardial infarction or admission for recurrent unstable angina was 42% in patients with increased C-reactive protein and cTnI, 4.5% in patients with increased cTnI and a normal C-reactive protein and 11% in patients with an abnormal C-reactive protein and a normal cTnI. Blood samples were taken on admission in patients admitted within 8 hours after the onset of symptoms, when increases in C-reactive protein attributable to myocardial necrosis are not yet expected (12).

A substantial proportion of patients in our present study with evidence of myocardial damage (an increase in troponin T within the first 24 hours) had an abnormal C-reactive protein and a troponin T below the cutoff on admission. In view of the time that C-reactive protein and troponin T remain increased after the onset of myocardial damage (days), these increases in C-reactive protein without concommittant increases in troponin T are not likely to be caused
by myocardial damage before the index episodes of chest pain that brought the patients to the hospital. The time course of increases in C-reactive protein and troponin T after the onset of myocardial damage may explain, however, why several studies have shown better independent prognostic information from C-reactive protein at discharge, when troponin T concentrations have returned to normal values(128;211). Our data are in accordance with a recent report by Liuzzo et al.(206) that showed that C-reactive protein 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 infarction requiring reperfusion therapy, there is no correlation between admission C-reactive protein and troponin T levels, 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.(206), but they do suggest that these relationships are complex.

Our data are in accordance with results from the GUSTO-IIa study that indicated that in a substantial proportion of patients, troponin T increased 8 and 16 hours after the baseline troponin T measurement(131). An early invasive treatment strategy was recently shown to be beneficial in high-risk patients identified by an increased troponin T(212), and in the MITI registry there was a significantly lower long-term mortality in patients admitted to hospitals favoring a very early (<6 hrs) invasive strategy(213). In the light of these findings, an increased troponin T measured early after admission may direct early treatment decisions, keeping in mind that patients with a troponin T 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 acute coronary syndrome, 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 “unheralded” or “heralded” myocardial infarctions.

Our data indicate that for increases in C-reactive protein to be an independent prognostic indicator in patients with an increased troponin T, only a short time window exists after the
onset of myocardial damage during which baseline C-reactive protein concentrations can be measured in most patients. In the majority of patients with baseline C-reactive protein values below the cutoff on admission, an increase in C-reactive protein 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 C-reactive protein measurements are preferably taken as soon as possible after the onset of symptoms, if possible within 8 hours. In contrast, increased troponin T is most reliably measured from 12 hours after the onset of symptoms. In that way, C-reactive protein measurements could be used in combination with troponin T 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)(214), especially in patients with a non-ST-elevation acute coronary syndrome.
Figure 1.

Median C-reactive protein (CRP) values during the first 24 hours after the onset of symptoms in two patient groups; group 1 (top): C-reactive protein on admission ≤3.0 mg/L; group 2 (bottom): C-reactive protein on admission >3.0 mg/L. Median values showed little change over the first 8 hours after the onset of symptoms in both groups.
Figure 2.
Median troponin T (TnT) (top) and C-reactive protein (CRP) (bottom) values and interquartile ranges during the first 24 hours after the onset of symptoms from the 38 patients in group 1 who received thrombolytic therapy (A) and the 37 patients in group 1 who did not receive thrombolytics (B). In both the patients with and without thrombolytic therapy, C-reactive protein values changed little in the first 8 hours after the onset of symptoms. Peak values in patients treated with thrombolytics were higher both for troponin T and C-reactive protein. Solid lines, median; dashed lines, interquartile ranges.

Figure 3.
Cumulative proportion of patients with an abnormal C-reactive protein (CRP) and troponin T (TnT) concentrations during the first 24 hours after the onset of symptoms. (A), patients who received thrombolytic therapy; (B), patients who did not receive thrombolytic therapy.
Figure 4.
Scatterplot of log-transformed C-reactive protein (CRP) and troponin T (TnT) values on admission, separated into patients who received thrombolytic therapy (closed dots) and patients who did not receive thrombolytics (open dots). Both the X and Y axis are log scale. Data points lying on the x axis indicate values that were below the detection limit. Dashed lines indicate the cutoff values: 3.0 mg/L for C-reactive protein and 0.1 μg/L for troponin T. C-reactive protein values on admission were below the cutoff more often in patients receiving thrombolytic therapy than in patients not receive thrombolytic therapy. However, substantial increases in C-reactive protein did occur in some patients with normal troponin T concentrations on admission, either with ST-elevation or without ST-elevation.
Table 1. Consecutive patients presented with chest pain, who had an abnormal troponin T (>0.1 μg/L) during the first 24 hours after the onset of symptoms

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(CRP ≤ 3.0 mg/L)</td>
<td>(CRP &gt; 3.0 mg/L)</td>
</tr>
<tr>
<td>n=75</td>
<td>n=81</td>
<td></td>
</tr>
<tr>
<td>Age (mean, range)</td>
<td>59 (35-90)</td>
<td>67 (36-88)*</td>
</tr>
<tr>
<td>Males (%)</td>
<td>51 (68%)</td>
<td>57 (70%)</td>
</tr>
<tr>
<td>Previous AMI</td>
<td>17 (23%)</td>
<td>21 (26%)</td>
</tr>
<tr>
<td>Previous PTCA</td>
<td>5 (7%)</td>
<td>7 (9%)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>6 (8%)</td>
<td>12 (15%)</td>
</tr>
<tr>
<td>Trombolitics</td>
<td>38 (51%)</td>
<td>23 (28%)†</td>
</tr>
<tr>
<td>CRP adm. (mg/L)</td>
<td>1.55 (0.6-2.0)</td>
<td>7.3 (5.2-13.0)*</td>
</tr>
<tr>
<td>TnT adm. (μg/L)</td>
<td>0.03 (0.01-0.1)</td>
<td>0.11 (0.03-0.2)‡</td>
</tr>
</tbody>
</table>

Patients are 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). Values for CRP and cTnT on admission are given as median and 25th and 75th percentiles.

AMI, acute myocardial infarction; CABG, coronary artery bypass grafting; CRP, C-reactive protein; PTCA, percutaneous transluminal coronary angioplasty; TnT, troponin T.