Early risk stratification in patients with chest pain
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Chapter 10

Different time frames for the occurrence of elevated levels of cardiac troponin T and C-reactive protein in patients with acute myocardial infarction

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ABSTRACT

The baseline plasma level of C-reactive protein is considered to be a parameter for risk stratification in patients with an acute coronary syndrome, independent of the level of cardiac Troponin T or cardiac Troponin I. However, myocardial tissue necrosis following prolonged arterial occlusion also induces release of C-reactive protein. Both phenomena may have their own kinetic behaviour with respect to changes in concentration of C-reactive protein. Therefore, in this study the time frame after onset of symptoms for measurement of C-reactive protein as an independent parameter is established. For this purpose, we evaluated patients with proven myocardial damage due to acute myocardial infarction with respect to changes of creatine kinase-MBmass, troponin T and C-reactive protein during 24 hours after onset of symptoms. Our results show that two subgroups can be discerned in patients with acute myocardial infarction: those with initially normal and those with already elevated concentration C-reactive protein on admission. Furthermore, based on the results of this study we conclude that for use of C-reactive protein as an independent prognostic parameter in patients with acute coronary syndrome, C-reactive protein should be measured in blood samples drawn as early as possible after the onset of symptoms to avoid contribution of a process of myocardial tissue necrosis, whereas estimation of troponin T should be performed at 6-12 hours.
INTRODUCTION

The level of C-reactive protein is considered to be an important prognostic indicator for early risk stratification in patients with acute coronary syndrome(130). However, the myocardial damage itself also induces C-reactive protein elevation in plasma(202). Therefore, the time interval after onset of symptoms during which the C-reactive protein can still be regarded as an independent prognostic parameter with respect to troponin T has to be established. To answer this question we studied patients with acute myocardial infarction. In this rather homogeneous group of patients, consecutive blood sampling might enable the contribution of tissue necrosis to the estimated levels of C-reactive protein during 24 hours after the onset of symptoms to be discerned.

MATERIALS AND METHODS

Patients
A total of 131 consecutive patients admitted to the Cardiac Emergency Department of the Academic Medical Center with acute myocardial infarction were included in this study. The protocol was approved by the institutional review board and all patients gave informed consent. The diagnosis of acute myocardial infarction was made when patients presented with typical chest pain suggestive of myocardial ischemia and evidence of myocardial damage by showing a typical creatine kinase-MB mass release curve in blood with a peak value >15 μg/l (2 times upper reference limit). 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.

Blood samples
Blood samples were drawn with an indwelling intravenous catheter at 3, 4, 5, 6, 7, 8, 12, 16, 20, 24 hours after onset of symptoms. Blood was collected in 10 ml heparin coated tubes and centrifuged without delay. The plasma was stored at -20 °C until further analysis.

Assay systems
Creatine kinase-MB\textsubscript{mass} assay was performed using the standard protocol on an ACS-180 analyzer (Bayer Diagnostics, Houten, the Netherlands). Troponin T was measured using the standard ELISA method on an ES300 analyzer (Roche, Almere, the Netherlands) with upper reference limit of 0.1 μg/l. C-reactive protein was measured with a standard assay on a Nephelometer analyzer (Behring Diagnostics, Marburg, Germany). The detection limit was 0.2 mg/l, upper reference limit used in this study was 3 mg/l.

RESULTS

Marker levels over time
Mean levels of creatine kinase-MB\textsubscript{mass}, troponin T and C-reactive protein during the first 24 hours after the onset of symptoms are shown in figure 1. Based upon their levels of C-reactive protein on admission, the patients could be split up into a group with normal C-reactive protein (≤ 3 mg/l) on admission (49/131: 37%; figure 1a) and a group with elevated C-reactive protein (> 3 mg/l) on admission (figure 1b), respectively. For both groups of patients creatine kinase-MB\textsubscript{mass} and troponin T peaked within 24 hours after onset of symptoms.

The patients admitted with normal C-reactive protein concentrations, initially showed normal levels of troponin T together with only slightly elevated creatine kinase-MB\textsubscript{mass} (figure 1a). In the next few hours troponin T and creatine kinase-MB\textsubscript{mass} showed a simultaneous rise. In contrast, increase of C-reactive protein occurred only slowly, reaching 9 mg/l, while the mean level of creatine kinase-MB\textsubscript{mass} and TnT peaked at t=12 hours (154 ± 20 μg/l (mean ± SEM)) and at t=16-20 hours (6.0 ± 0.7 μg/l (mean ± SEM)), respectively. The number of patients with elevated C-reactive protein increased linearly in time during 24 hours after onset of symptoms, thus showing totally different kinetics with respect to troponin T and creatine kinase-MB\textsubscript{mass} (figure 2).

For patients with already elevated levels of C-reactive protein on admission (11.9 ± 2.3 mg/l (mean ± SEM), figure 1b), there was initially no further increase of C-reactive protein levels. About 16 hours after onset of symptoms some increase could be discerned which, unlike the patients entering with normal C-reactive protein, soon levelled off at 20.3 ± 3.0 mg/l (mean ± SEM). The levels of troponin T (maximum level at t=20 hours: 4.7 ± 0.7 μg/l (mean ± SEM)) and creatine kinase-MB\textsubscript{mass} (maximum level at t=16 hours: 119 ± 16 μg/l (mean ± SEM)) showed similar kinetics as for the group of patients with
normal C-reactive protein on admission, although the decline in levels of creatine kinase-MB\text{mass} was less pronounced.

**DISCUSSION**

This study shows that patients with an acute myocardial infarction can be divided into two subgroups: those with normal and those with elevated C-reactive protein on admission, respectively. In both groups a rise in levels of C-reactive protein about 16 hours after the onset of symptoms can be discerned, most probably due to the cardiac incident itself. The different release patterns of troponin T and C-reactive protein in patients with a normal C-reactive protein on admission (delayed onset of rise, much slower rise of C-reactive protein with respect to troponin T) are clearly indicative for different release kinetics of C-reactive protein and troponin T. In fact, C-reactive protein is not released as a direct result of myocardial damage, but as a consequence of the induction of its synthesis by the liver, triggered by interleukine 6(215). Eventually, all patients show elevated levels of C-reactive protein, probably as a direct result of the release of cytokines in the inflammatory process induced by the myocardial tissue damage following arterial occlusion.

An elevated level of C-reactive protein on admission without a concomitant elevation in troponin T may point to the presence of an already existing, eventually chronic, cardiovascular inflammatory process. This inflammatory state is apparently not accompanied by the leakage of troponin T and creatine kinase-MB\text{mass} out of the cardiomyocytes into the plasma, as these levels are normal (troponin T) or only slightly elevated (creatine kinase-MB\text{mass}) on admission. When this pre-existent condition eventually culminates into an acute myocardial infarction, levels of troponin T and creatine kinase-MB\text{mass} tend to reach less elevated levels as compared to the patients entering with normal C-reactive protein. Possibly the occurrence of acute myocardial infarction in concordance with initially normal C-reactive protein follows a more devastating course with respect to the extent of cardiac tissue necrosis. This would also explain the ever increasing levels of C-reactive protein in this group of patients. However, further investigation is needed to prove this hypothesis. With respect to the patients' outcome, an abnormal C-reactive protein on admission in patients suffering from unstable angina or non- Q wave myocardial infarction is associated with increased risk of a major cardiac event within 6 months(12). The results of the present study support the increasing
evidence of C-reactive protein as an independent prognostic indicator for patients with acute myocardial infarction. Moreover, our results indicate that for C-reactive protein to be a prognostic indicator for patients with an acute coronary syndrome independent of troponin T, blood samples should be drawn as soon as possible after the onset of symptoms (figure 2), whereas troponin T measurements should be performed at 6-12 hours.
Figure 1.
Plasma levels of creatine kinase-MB_{\text{mass}} (CK-MB_{\text{mass}}), troponin T (cTnT) and C-reactive protein (CRP) in the first 24 hours after acute myocardial infarction. Concentrations of creatine kinase-MB_{\text{mass}}, troponin T and C-reactive protein were estimated in blood samples drawn at 3, 4, 5, 6, 7, 8, 12, 16, 20 and 24 hours after the onset of symptoms. Values are given as mean ±SEM for patients with initial normal levels of C-reactive protein (≤ 3 mg/l, figure 1a) and elevated C-reactive protein (> 3 mg/l, figure 1b).
Different time frames

Figure 2.
Cumulative number of patients with elevated C-reactive protein (CRP), troponin T (cTnT) and creatine kinase-MB mass (CK-MBmass). For the group patients showing normal levels of C-reactive protein on admission, for each parameter the cumulative percentage is shown for the number of patients exceeding upper reference limit (C-reactive protein and troponin T) and 2 times upper reference limit (creatine kinase-MBmass), respectively.