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Original paper

MARKERS OF MYOCARDIAL DAMAGE AND INFLAMMATION IN PATIENTS WITH CORONARY ARTERY DISEASE

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Summary: To shed light on the clinical significance of elevated CRP levels we performed a comparative analysis of the predictive values of both CRP and TnT in patients with unstable coronary artery disease for the occurrence of major cardiac events within 6 months. CRP and Troponin T were measured on admission in patients with acute coronary syndromes without ST segment elevation. Patients were treated according to a conservative management and the incidence of major cardiac events within 6 months was assessed. A total of 73 patients were included in the study. There were 27 major cardiac events (37%). An abnormal CRP (>4 mg/L) and an abnormal TnT (> 0.01 mg/L) were present in 36 patients (49.3%). The incidence of a major cardiac event was significantly higher among patients with CRP > 4 mg/L than in other patients (63.9 vs 10.8%), and this was evident both in patients with an elevated TnT (85.7 vs 20%) and in those without an elevated TnT (33.3 vs 4.5%). The sensitivity of a concentration of CRP > 4 mg/L for predicting a future ischaemic event was 85%, with a specifity of 72% and negative predictive value of 89%. For TnT > 0.01 mg/L the sensitivity was 77%, specifity 67% and negative predictive value 84%. The present study shows that both CRP, a non-specific acute phase reactant, and TnT, a cardiac specific marker of myocardial damage, are elevated early in a substantial number of patients with acute coronary syndromes. It shows that CRP and TnT are independent prognostic indicators of adverse ischaemic events.

Key words: inflammation, CRP, acute coronary syndromes, troponins

Introduction

Inflammatory mechanisms play a pivotal role in the atherosclerotic process. At the base of atherogenesis there are complex interactions between macrophages, T lymphocytes and smooth muscle cells. A growing body of experimental evidences suggest that inflammation is involved in the pathogenesis of acute coronary syndromes (ACS) and influences their clinical evolution.

In fact, in patients with ACS, coronary atherosclerotic plaques are characterized by an abundant inflammatory infiltrate. Moreover, in these patients systemic signs of inflammatory reaction can be observed: activated circulating inflammatory cells (neutrophil, monocytes and lymphocytes) and increased concentrations of pro-inflammatory cytokines, such as interleukin (IL)-1 and 6, and acute phase reactants, in particular C-reactive protein (CRP).

Recent data demonstrate that CRP is a strong independent predictor of adverse cardiac events and death in patients with ACS, but also in patients with stable ischaemic heart disease and in apparently healthy men and women. Furthermore, CRP is an important prognostic index, for early and late outcome, in patients undergoing percutaneous coronary interventions, and may be useful in choosing the therapeutic management of the patient. Although the causes of inflammation in patients with ACS are not yet clear, this new line of research may open the way to a different clinical approach for these patients

For the patients with acute coronary syndromes (i.e. unstable angina or non-Q-wave myocardial infarction) the main pathophysiologic mechanisms, in the form of plaque rupture or erosion, are followed by exposure of thrombogenic contents, such as collagen to the circulation (1). The resulting platelet activation

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and adhesion promote thrombus formation. Pathohistologic studies have disclosed focal cell necrosis distal in the myocardium supplied by the culpit artery, which have been attributed to repetitive embolization from such friable thrombi (1, 2). The resulting minor myocardial damage leads to troponin T (TnT) or I(TnI) release in about one third of such patients. Although enzyme activity of creatine kinase (CK) remains within the normal range, there is a five-to-ten fold higher incidence for the mortality and myocardial infarction during the 30 day follow-up period for such TnT-positive patients (1–3).

Over the past two decades many experimental and clinical studies have examined the role of inflammatory process in the initiation and progression of atherosclerosis (4, 5). Several of the acute-phase proteins, which serve as nonspecific markers of the human inflammatory response, have been found to be elevated across the clinical spectrum of atherosclerotic coronary artery disease. Furthermore, increased concentrations of the acute phase reactant C-reactive protein (CRP) appear to be predictive of a higher risk for long-term cardiovascular morbidity/mortality in patients with acute coronary syndromes (6), as well as in asymptomatic patients at risk for coronary artery disease (7, 8). This potential predictive capacity of CRP warrants further evaluation alone and in conjunction with established serum cardiac markers.

The aim of this study was to examine the prognostic value of C-reactive protein and Troponin T in patients with unstable angina or non Q-wave myocardial infarction for the occurrence of major cardiac events within six months.

Methods and Methods

Patients

Eligible for the inclusion in the study were men and women with acute coronary syndromes without persistent ST-segment elevation, admitted to coronary care units with typical chest pain < 12 hour duration. Patients were included if they had either diagnostic ST-segment depression or T-wave changes characteristic of myocardial ischaemia.

The diagnosis of acute myocardial infarction was established according to the WHO criteria: severe ischaemic chest pain of ± 20 minutes duration, a diagnostic ECG and an increase in CK above the upper reference limit in hospital in at least two consecutive samples.

Patients with ST-elevation in electrocardiogram on admission that were candidates for reperfusion therapy (either primary PTCA or thrombolytic therapy) were excluded. Patients were also excluded when the evolution in the electrocardiogram showed the development of new left bundle branch block or new Q waves. Other exclusion criteria were a known or suspected infection, inflammatory or neoplastic conditions, erythrocyte sedimentation rate > 20 mm/h, recent (<3 months) major trauma, surgery, myocardial infarction or coronary revascularization.

Assays

CRP and TnT were measured from samples drawn on admission (overage within 12 hours of the onset of chest pain) and results were kept blinded from the physicians treating the patients. Blood samples were drawn in vacuum tubes, centrifuged and remained serum stored at –20 °C for later measurements. Patients were treated with aspirin, heparin *i.v*, nitrates i.v, β blockers etc, according to a conservative management strategy as outlined in the TIMI IIb trial.

C-reactive protein was measured with a nephelometric assay (Roche Diagnostics GmbH, Mannheim, Germany). The detection limit was 3 mg/L, measurement range 3–240 mg/L. The 95th percentile in 20 healthy individuals in our institution was established at 4.0 mg/L.

Troponin T was measured with an electrochemiluminescence immunoassay (ECLIA) in Elecsys 1010 (Roche Diagnostics GmbH, Mannheim, Germany). The lower detection limit was 0.010 mg/L, ranging from 0.010 to 20 μg/L. The upper limit of normal according to the manufacturer was 0.010 μg/L.

Follow-up

A six-month follow-up was assessed by regular clinical examination for every month. Primary outcome was defined as cardiac death, new non-fatal myocardial infarction or recurrent hospital admission for severe unstable angina (defined as recurrent unstable angina at rest with diagnostic ST-segment depression or T-wave changes characteristic of myocardial ischaemia).

Statistical analysis

CRP and TnT were treated as a dichotomous variable (either elevated or normal) with cut-off value of 4.0 mg/L for CRP and of 0.010 mg/L for TnT. Two-by-two contingency tables for the primary outcome were constructed for CRP > 4.0 mg/L, TnT > 0.010 mg/L or both elevated. The prognostic value of CRP and TnT was assessed in a multivariate logistic regression model with the primary outcome as the dependent variable. To assess avant-free survival, Kaplan-Meier's curves were constructed for the primary outcome and differences in mean survival were compared using the log-rank test. Calculations were done with a statistical software package (SPSS 9.0 for Windows, SPSS, USA). All statistical comparisons were two-tailed.

Results

A total of 73 patients were included in the study, 55 patients with unstable angina and 18 patients with non-Q wave myocardial infarction. The patients' characteristics are summarized in *Table I*, comparing patients that reached a primary endpoint with the other patients.

Follow-up at six month was 100% complete. There were 27 major cardiac events (36.9%) listed in *Table II*.

An abnormal CRP (>4.0 mg/L) was present in 36 patients (49.3%), median CRP in 27 patients with major cardiac events of 33.7 mg/L (range 3–178 mg/L), compared to 6.51 (range 3–141 mg/L) of 46 patients without a major cardiac event, $p<0.001$.

Troponin T values ranged from <0.010 to 3.91 mg/L. An abnormal TnT > 0.010 mg/L was present in 36 patients (49.3%), median TnT in 27 patients with a major cardiac event of 0.73 (range 0.01 to 3.91 μg/L), compared to 0.12 μg/L (range 0.01 to 2.20 μg/L) in 46 patients without events, $p<0.001$.

As *Table I* shows, there are no significant differences in the baseline characteristics (sex, age, hypertension, smoking, previous myocardial infarction) between the two groups, except for C-reactive protein and Troponin T.

The incidence of a major cardiac event was significantly higher among patients with CRP > 4 mg/L, than in other patients (63.9% vs 10.8 %), and this was evident both in patients with an elevated troponin T (85.7 vs 20%) and in those without an elevated TnT (33.3 vs 4.5%) (*Figure 1*).

Table I Baseline characteristics

	No events n (%)	Death/AMI/UAP n (%)
Number of patients	46	27
Males	26 (56.5)	14 (48.1)
Age	58.19 (± 9.06)	58.14 (± 9.90)
Hypertension	34 (73.9)	17 (63.7)
Smoking	16 (34.8)	11 (40.7)
Prev. AMI	12 (26.1)	7 (25.9)
Cholesterol, mmol/L	6.28	6.16
CRP > 4.0 mg/L	13 (28.3)	23 (85.2)#
TnT >0.010 mg/L	15 (32.6)	21 (77.8)#
Ejection fraction %	59.28	58.88

Differences between groups were compared with the x^2 statistic, differences in means were compared with the t-test.
# Categories for which $p<0.001$
AMI= Acute Myocardial Infarction
PTCA= Percutaneous Transluminal Coronary Angioplasty
CABG= Coronary Artery Bypass Grafting
CRP= C-reactive protein
TnT= Troponin T

Table II Events during a 6 month follow-up in 73 patients with unstable angina and non-Q wave myocardial infarction

Events	N	(%)
Cardiac death	3	4.1
Recurrent AMI	16	21.9
Recurrent UA	8	11.0
Total	27	36.9

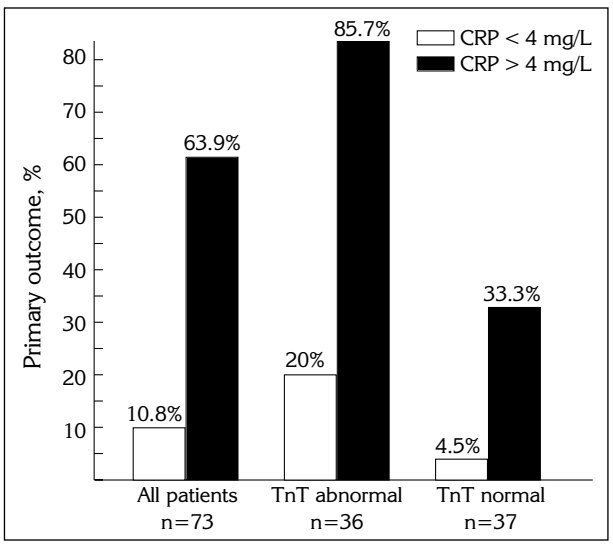

Figure 1. Incidence of major cardiac complications by normal or abnormal CRP concentration in all patients and in those with a normal and abnormal troponin T concentration. Primary outcome was defined as cardiac death, non-fatal myocardial infarction or admission for recurrent unstable angina.

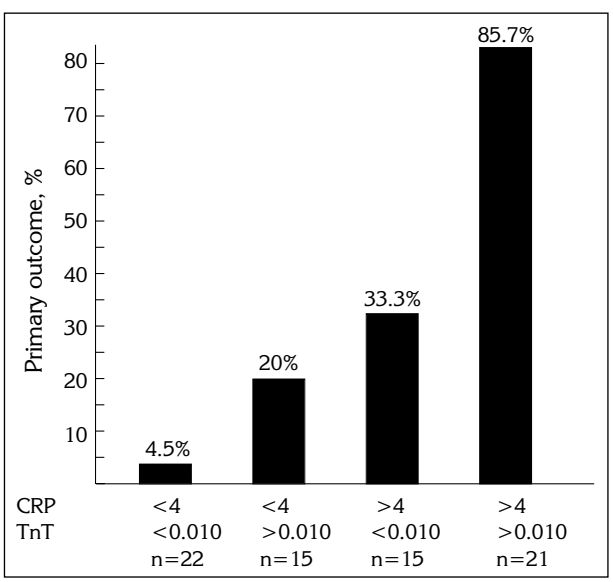

Figure 2. Risk stratification of patients with acute coronary syndromes without persistent ST-segment elevation according to CRP (mg/L) and TnT (μg/L) concentration.

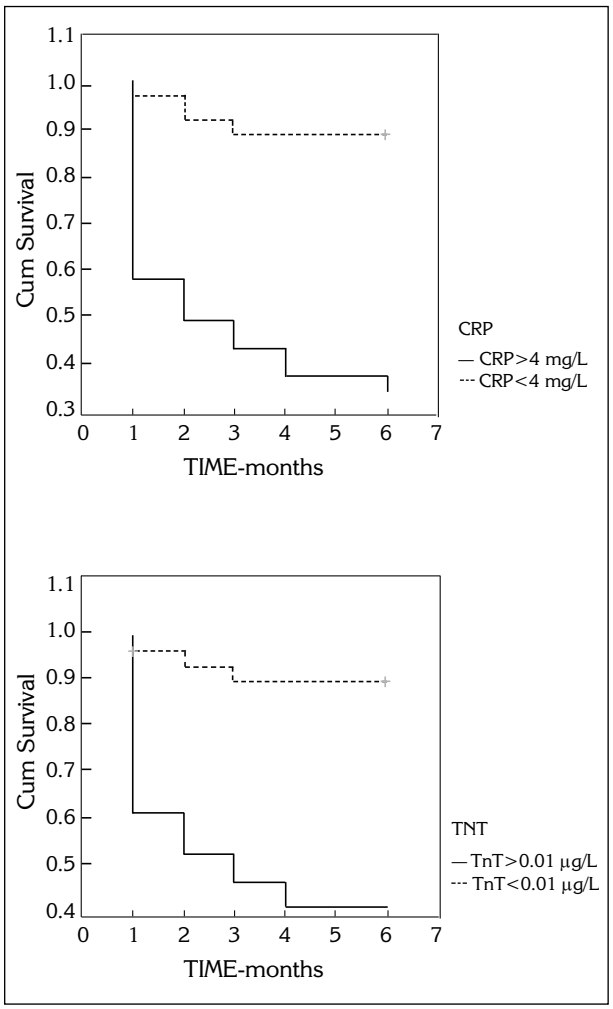

Figure 3. Kaplan-Meier's survival curves for 73 patients with acute coronary syndromes during a follow-up of six months according to a CRP (above) and cTnT (below)

The multivariate model with age, gender, history of infarction and hypertension significantly improved when either an abnormal CRP or an abnormal TnT or both were included in the model, demonstrating the additive prognostic value of both markers. A multivariate model including both markers showed improved performance in comparison with models with a single marker, demonstrating their independent predictive value.

Figure 2 shows the event rate in patients having both CRP and TnT elevation, either CRP or TnT elevated, or no CRP or TnT elevation.

The incidence of the combined endpoint cardiac death, non-fatal myocardial infarction and recurrent severe unstable angina were significantly more frequent in patients having both CRP/TnT elevated (18/21), than in patients having either (8/30) or none elevated (1/22) (CRP/TnT) (*Table III*). Kaplan-Meier's survival analysis showed that mean event-free survival for the primary outcome was significantly lower in

Table III Number of events in patients with no CRP or TnT elevations, either CRP or TnT elevated or both parameters elevated

	No elevation	Either CRP/TnT		Both CRP/TnT
		TnT>0.01 CRP<4	TnT<0.01 CRP>4	
N	22	15	15	21
Death/MI/UA	1	3	5	18

patients having CRP/TnT elevated versus patients with no elevation (*Figure 3*, logrank test 23.72 and 14.41 respectively, $p<0.0001$). The sensitivity of a concentration of CRP>4 mg/L for predicting a future ischaemic event was 85% with a specificity of 72% and negative predictive value of – 89%. For the troponin T > 0.01 µg/L the sensitivity was 77% with a specificity of 67% and negative predictive value of 84%.

Discussion

The present study confirms earlier studies showing that both CRP, a non-specific acute phase reactant, and TnT, a cardiac specific marker of myocardial damage, are elevated early in a substantial number of patients with unstable angina and non-Q wave myocardial infarction. It shows that CRP and TnT are independent prognostic indicators of adverse outcome. The incidence of major cardiac events was 63.9% in patients with an abnormal CRP vs 10.8% in patients with a normal CRP. Moreover, in patients without a TnT elevation, a CRP > 4.0 mg/L carried a significantly higher risk for a major cardiac event within 6 months (33.3 vs 4.5 %). Patients with both CRP and TnT elevated had the highest incidence of cardiac death, recurrent AMI or admission for recurrent unstable angina within 6 months. In contrast, patients with both a normal CRP and TnT have an excellent prognosis. In this patients group, there was only one readmission for recurrent unstable angina during the 6-month follow-up.

Our study confirms the findings of the recent reports from the TIMI 11A substudy (9) and CAPTURE trial (10), which demonstrated independent and combined prognostic value of an abnormal CRP and TnT tests for the prediction of an unfavorable short-term outcome in patients with acute coronary syndromes. These findings strengthen the evidence that an inflammatory process is critical in the pathogenesis of ACS and suggests that the intensity of the inflammatory response can influence the clinical outcome.

In conclusion, our study demonstrates the independent prognostic value of CRP and TnT in patients with unstable angina or non-Q myocardial infarction, for short term adverse outcome. These findings suggest that the effect of a comprehensive treatment, e.g. with IIb/IIIa antagonists and anti-inflammatory treatment, of patients with both markers elevated or early discharge of patients with both a normal CRP and TnT could be studied in a prospective study (5).

MARKERI OŠTEĆENJA MIOKARDA I INFLAMACIJE U PACIJENTA SA KORONARNIM ARTERIJSKIM OBOLJENJEM

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Kratak sadržaj: Da bi se procenio klinički značaj povećanih vrednosti CRP izvedena je uporedna analiza prediktivnih vrednosti CRP i TnT u pacijenta sa nestabilnim koronarnim arterijskim oboljenjem koji su imali velike srčane promene u poslednjih 6 meseci. CRP i troponin T su mereni pri prijemu pacijenata sa akutnim koronarnim sindromom bez elevacije ST segmenta. Pacijenti su tretirani konzervativnim postupkom i praćena je učestalost većih srčanih promena u toku 6 meseci. U studiju su bila uključena 73 pacijenta. Registrovano je 27 većih srčanih promena (37%). Patološki CRP (>4 mg/L) i patološki TnT (> 0,01 mg/L) su nađeni kod 36 pacijenta (49,3%). Učestalost velikih srčanih promena bila je značajno veća među pacijentima sa vrednošću CRP > 4 mg/L nego u drugih pacijenata (63,9 vs. 10,8%), što je bilo očigledno i u pacijenata sa povišenim TnT (85,7 vs. 20%) i onih bez povišenja TnT (33,3 vs. 4,5%). Osetljivost koncentracije CRP > 4 mg/L za predviđanje budućih ishemijskih događaja bila je 85%, sa specifičnošću od 72% i negativnom prediktivnom vrednošću od 89%. Za TnT > 0,01 mg/L osetljivost je bila 77%, specifičnost 67% i negativna prediktivna vrednost 84%. Izloženo proučavanje pokazuje da su CRP, ne-specifični akutno fazni reaktant i TnT, srčani specifični marker oštećenja miokarda povišeni rano u određenom broju pacijenata sa akutnim koronarnim sindromima. To ukazuje da su CRP i TnT nezavisni prognostički indikatori ishemijskih događaja.

Ključne reči: inflamacija, CRP, akutni koronarni sindromi, troponini

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