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...
and adhesion promote thrombus formation. Patho-
histologic studies have disclosed focal cell necrosis
distal in the myocardium supplied by the culprit 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 (Tnl)
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 inci-
dence for the mortality and myocardial infarction dur-
ing 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 inflam-
matory process in the initiation and progression of ath-
erosclerosis (4, 5). Several of the acute-phase pro-
tiens, which serve as nonspecific markers of the hu-
man inflammatory response, have been found to be
elevated across the clinical spectrum of atherosclerot-
ic 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 pa-
ients with acute coronary syndromes (6), as well as in
asymptomatic patients at risk for coronary artery di-
sese (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 prog-
nostic value of C-reactive protein and Troponin T in
patients with unstable angina or non Q-wave myocar-
dial 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 characteris-
tic 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 con-
secutive 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 de-
velopment of new left bundle branch block or new Q
waves. Other exclusion criteria were a known or sus-
ppected infection, inflammatory or neoplastic condi-
tions, erythrocyte sedimentation rate > 20 mm/h,
recent (<3 months) major trauma, surgery, myocar-
dial 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 sam-
ple were drawn in vacuum tubes, centrifuged and
remained serum stored at −20 °C for later measure-
ments. 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 nephelo-
metric assay (Roche Diagnostics GmbH, Mannheim,
Germany). The detection limit was 3 mg/L, measure-
ment 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 electrochemi-
oluminescence 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 out-
come was defined as cardiac death, new non-fatal
myocardial infarction or recurrent hospital admission
for severe unstable angina (defined as recurrent unsta-
able angina at rest with diagnostic ST-segment depres-
sion 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 regres-
sion model with the primary outcome as the depend-
ent variable. To assess avant-free survival, Kaplan-
Meier’s curves were constructed for the primary out-
come 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

<table>
<thead>
<tr>
<th></th>
<th>No events</th>
<th>Death/AMI/UAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>46 (62.8)</td>
<td>27 (37.2)</td>
</tr>
<tr>
<td>Males</td>
<td>26 (56.5)</td>
<td>14 (43.5)</td>
</tr>
<tr>
<td>Age</td>
<td>58.19 (± 9.06)</td>
<td>58.14 (± 9.90)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>34 (73.9)</td>
<td>17 (63.7)</td>
</tr>
<tr>
<td>Smoking</td>
<td>16 (34.8)</td>
<td>11 (40.7)</td>
</tr>
<tr>
<td>Prev. AMI</td>
<td>12 (26.1)</td>
<td>7 (23.9)</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>6.38</td>
<td>6.16</td>
</tr>
<tr>
<td>CRP &gt; 4.0 mg/L</td>
<td>13 (28.3)</td>
<td>23 (52.2)%#</td>
</tr>
<tr>
<td>TnT &gt;0.010 mg/L</td>
<td>15 (32.6)</td>
<td>21 (77.8)%#</td>
</tr>
<tr>
<td>Ejection fraction %</td>
<td>59.28</td>
<td>58.88</td>
</tr>
</tbody>
</table>

Differences between groups were compared with the x² 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

<table>
<thead>
<tr>
<th>Events</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac death</td>
<td>3</td>
<td>4.1</td>
</tr>
<tr>
<td>Recurrent AMI</td>
<td>16</td>
<td>21.9</td>
</tr>
<tr>
<td>Recurrent UA</td>
<td>8</td>
<td>11.0</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>36.9</td>
</tr>
</tbody>
</table>

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.
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.

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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 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%.

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

<table>
<thead>
<tr>
<th></th>
<th>No CRP/TnT</th>
<th>Either CRP/TnT</th>
<th>Both CRP/TnT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP/TnT&gt;4.0</td>
<td>15</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>CRP/TnT&lt;4.0</td>
<td>15</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>Death/MI/UA</td>
<td>1</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

### 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 Ilb/Ilia 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

Anna Tzontcheva¹, Arman Postadjian²

¹Chair of Clinical Laboratory and Clinical Immunology, Medical University, Sofia, Bulgaria
²Department of Internal Medicine, University Hospital »St. Anne«, Sofia, Bulgaria

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 pacijentac 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 pacijentac (63,9 vs. 10,8%), što je bilo očigledno i u pacijentac sa povišenim TnT (85,7 vs. 20%) i onih bez povišenja TnT (33,3 vs. 4,5%). Učestalost koncentracije CRP > 4 mg/L za previdanje budućih ishemijskih događaja bila je 85%, sa specifičnošću od 72% i negativnom prediktivnom vrednošću od 89%. Za TnT > 0,01 mg/L učestalost je bila 77%, specifičnost 67% i negativna prediktivna vrednost 84%. Isto tako, proučavanje pokazuje da su CRP, ne-specificni akutno fazni reaktant i TnT, srčani specifični marker oštećenja miokardia u određenom broju pacijentac sa akutnim koronarnim sindromima. To ukazuje da su CRP i TnT nezavisni prognoštni indikatori ishemijskih događaja.

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

References


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