JMB 2008; 27 (1) DOI: 10.2478/v10011-007-0045-1

UDK 577.1 : 61 **ISSN 1452-8258**

JMB 27: 35–39, 2008

Original paper
Originalni naučni rad

C-REACTIVE PROTEIN IN ESTIMATING INFLAMMATORY STATUS IN PATIENTS WITH ACUTE CORONARY SYNDROME

C-REAKTIVNI PROTEIN U PROCENI STEPENA INFLAMACIJE KOD PACIJENATA S AKUTNIM KORONARNIM SINDROMOM

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Summary: Chronic inflammation plays a key role in the pathogenesis of atherosclerosis, and is considered as a risk factor for the occurrence of acute coronary events, together with traditional risk factors such as age, smoking, hypercholesterolemia, diabetes mellitus and genetic predisposition. In this study, inflammatory status was estimated in patients with acute coronary syndrome. C-reactive protein, erythrocyte sedimentation rate and white blood cell count were measured at admission to the hospital in 25 patients with unstable angina pectoris and 31 patients with acute myocardial infarction, and compared with healthy control group (n = 59). C-reactive protein was the only parameter that differed significantly between all three groups ($p < 0.0001$), and patients with unstable angina had higher levels (median 7.28 mg/L) than patients with myocardial infarction (4.10 mg/L) and control group (1.07 mg/L). The obtained results show that levels of chronic inflammation in patients with acute coronary syndrome are significantly higher than baseline inflammation levels in a healthy population.

Keywords: acute coronary syndrome, acute myocardial infarction, C-reactive protein, inflammation, unstable angina pectoris

Kratak sadržaj: Hronična inflamacija ima ključnu ulogu u patogenezi ateroskleroze i smatra se jednim od faktora rizika za pojavu kardiovaskularnih bolesti, zajedno sa tradicionalnim faktorima rizika kao što su godine starosti, pušenje, *diabetes mellitus* i genetska predispozicija. U ovom radu ispitivan je inflamatorni status pacijenata s akutnim koronarnim sindromom. C-reaktivni protein, brzina sedimentacije eritrocita i broj leukocita određeni su na prijemu u bolnicu kod 25 pacijenata s nestabilnom anginom pektoris i 31 pacijenta s akutnim infarktom miokarda, i upoređeni sa kontrolnom grupom zdravih ljudi (n = 59). C-reaktivni protein je jedini parametar koji se statistički značajno razlikovao između svih grupa ($p < 0,0001$), pri čemu su vrednosti kod pacijenata s nestabilnom anginom bile veće (medijana 7,28 mg/L) od vrednosti kod pacijenata s infarktom miokarda (4,10 mg/L) i kontrolne grupe (1,07 mg/L). Dobijeni rezultati pokazuju da je stepen hronične inflamacije pacijenata s akutnim koronarnim sindromom veći od bazalnih nivoa zdrave populacije.

Ključne reči: akutni koronarni sindrom, akutni infarkt miokarda, C-reaktivni protein, inflamacija, nestabilna angina pektoris

Introduction

Coronary plaque disruption is the most important mechanism by which atherosclerosis leads to the acute coronary syndrome (ACS) of unstable angina (UA) and acute myocardial infarction (AMI). In the last few decades, there was substantial evidence that the inflammatory process plays an important role in the pathogenesis of atherosclerosis. ACS, stroke and peripheral arterial occlusion result from a chronic inflammatory

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List of abbreviations:
ACS – acute coronary syndrome
AMI – acute myocardial infarction
CRP – C-reactive protein
ESR – erythrocyte sedimentation rate
UA – unstable angina
WBC – white blood cells

process, as well as from disorders of lipid metabolism, modified by genetic and environmental factors (1). Numerous studies have identified elevated levels of markers of inflammation as risk indicators for future cardiovascular events in patients with ACS. Of these markers, C-reactive protein (CRP) has been the most widely studied. It was shown that CRP levels at the time of presentation or at hospital discharge provide prognostic information on both short-term and long-term risk, even in the absence of troponin elevation (2–8).

The aim of this study was to estimate inflammatory status in patients with ACS, i.e. unstable angina and myocardial infarction with ST elevation. In order to do this, inflammatory parameters: CRP, white blood cells (WBC) count and erythrocyte sedimentation rate (ESR) on admission to the hospital were compared with levels in the healthy referent group.

Materials and Methods

The study population included 25 patients with unstable angina pectoris and 31 patients with myocardial infarction with ST elevation, admitted to the Intensive Care Unit of the General Hospital Bor. None of the patients had any sign of interfering noncardiac diseases, such as inflammatory disorders, malignancy, infection, recent surgery or trauma. Referent group included 59 healthy individuals on their regular annual medical control in the Occupational Diseases Unit at the Health Center Bor.

Venous blood samples were obtained on admission, for patients with AMI up to 12 hours after symptom onset. WBC count (measured as part of the full blood count), ESR, creatine kinase (CK), CK-MB, glucose, cholesterol, HDL-cholesterol and triglycerides were determined immediately after venepuncture by standard methods. Serum samples for CRP determination were stored at –20 °C and assayed in a single batch at the end of the study. CRP was measured by N High Sensitivity CRP test performed on a Behring BNTM II Nephelometer (Dade Behring Marburg GmbH, Germany) using polystyrene particles coated with mouse monoclonal antibodies to CRP. The detection limit of the assay was 0.175 mg/L for measurements performed using a sample dilution of 1:20, and upper reference limit assigned by the manufacturer was 2.87 mg/L.

During the in-hospital stay, following relevant data were obtained for each patient: age, sex, smoking status, body-mass index, previous history of hypertension and diabetes mellitus. All patients gave their informed consent for participating in the study.

Continuous variables are described as mean or median values, according to the manner of distribution. Comparison between the groups was performed with Kruskal-Wallis and Mann-Whitney tests for continuous variables, and χ^2-test for categorical variables. For all tests, a two-tailed p value < 0.05 was considered statistically significant. All statistics were performed on Statistica®, StatSoft Inc, 1999, USA.

Table I Comparison data of study groups.

Parameter	Group			P
	Control n=59	UA n=25	AMI n=31	
Age, years	40.5	58.0	58.6	<0.0001
Male, (%)	58	60	77	NS
Smokers, (%)	44	36	48	NS
Hypertension, (%)	20	72	45	<0.0001
Diabetes mellitus, (%)	0	12	13	0.0089
BMI, kg/m^2	25.8	27.2	26.5	NS
Glucose, mmol/L	4.93	5.63	6.33	0.0014
Cholesterol, mmol/L	5.81	5.25	5.82	NS
HDL-cholesterol, mmol/L	1.23	0.82	0.89	<0.0001
Triglycerides, mmol/L	1.26	1.86	1.50	0.0231
CK, U/L	83	68	167	0.0001
CK-MB, U/L	6.7	5.7	18.4	<0.0001
ESR, mm/h	14.7	25.3	15.0	0.0012
WBC count, 109/L	6.62	6.74	8.00	0.0031
CRP, mg/L	1.07	7.28	4.10	<0.0001

Continuous variables are mean or median values, according to the manner of distribution. NS indicates not significant.

Table II Significance of differences between the pairs of groups.

Parameter	p		
	Control : UA	Control : AMI	UA : AMI
Age	<0.0001	<0.0001	NS
Hypertension	<0.0001	0.0261	NS
Diabetes mellitus	0.0388	0.0223	NS
Glucose	0.0476	0.0004	NS
HDL-cholesterol	<0.0001	<0.0001	NS
Triglycerides	0.0105	NS	0.0492
CK	NS	0.0001	0.0001
CK-MB	NS	<0.0001	<0.0001
ESR	0.0002	NS	0.0320
WBC count	NS	0.0017	0.0041
CRP	<0.0001	<0.0001	0.0141

NS indicates not significant.

Results

Comparison data for the groups of patients with UA and AMI and control subjects are presented in *Table I*. Significant difference was shown for following parameters: age, hypertension, history of diabetes mellitus, glucose, HDL-cholesterol, triglycerides, enzymes and inflammatory markers. Significance of differences between the pairs of groups for these parameters is presented in *Table II*. Between the patients with UA and AMI no difference was shown for: age, history of hypertension and diabetes, and levels of glucose and HDL-cholesterol. UA patients had higher levels of triglycerides and higher ESR than other two groups. AMI patients had higher WBC count and heart enzymes levels than UA patients and control subjects.

The only parameter that differed significantly between all three groups was CRP (*Tables I* and *II*, *Figure 1*), with the highest levels in UA patients. As CRP was shown to correlate with age (9, 10), and the control group in this study was significantly younger, another comparison was done, including subjects 40–55 years of age from each group (28 controls, 12 UA, 16 AMI). Again, it was shown that CRP differed significantly between these subgroups ($p = 0.0008$), as well as between the pairs of subgroups (control : UA, $p = 0.0002$; control : AMI, $p = 0.0233$; UA : AMI, $p = 0.0328$).

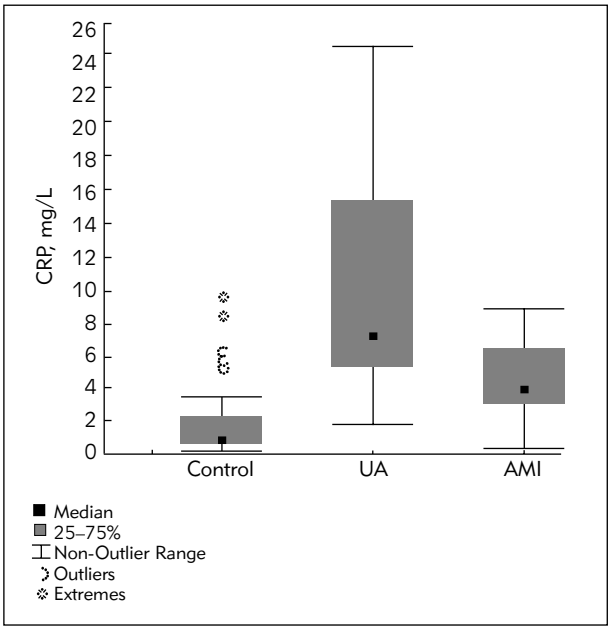

Figure 1 CRP distribution in the examined groups.

Discussion

It is widely accepted that inflammation plays a key role in the pathogenesis of atherosclerosis (11). Chronic inflammatory process can develop into an acute clinical event by induction of plaque rupture and thrombosis. Chronic inflammation is therefore considered as a risk factor for the occurrence of acute coronary events, together with traditional risk factors such as age, smoking, hypercholesterolemia, diabetes mellitus and genetic predisposition (2–7, 12–15).

In this study we investigated inflammatory status in patients with unstable angina pectoris and myocardial infarction with ST elevation. CRP and other parameters were measured at admission to the hospital, for patients with AMI up to 12 hours after the onset of chest pain. In most of the patients, CRP levels in serum rise after 12 hours of symptom onset (16), so it can be assumed that levels on admission reflect baseline inflammation. This study shows, in accordance with earlier studies (3, 17), that patients with ACS have higher levels of CRP than control subjects, and also,

that UA patients have significantly higher levels of CRP (7.28 mg/L) than AMI patients (4.10 mg/L). It should be noted that in patients with UA time from symptom onset to admission was longer and not reported as precisely as in patients with AMI. This fact may explain higher levels of CRP and ESR in patients with UA. Also, it can be speculated that multiple minor myocardial injuries in UA patients are responsible for higher CRP than in AMI patients at admission, in spite of their major event and intense inflammation (elevated WBC count).

It cannot be, of course, concluded from these results whether CRP levels are triggers or just indicators of cardiovascular events, and results from *in vitro* experiments and animal models are controversial (18–21). However, ongoing works show that specific inhibitors of CRP, such as 1,6-bis(phosphocholin)-hexane, can be beneficial in the treatment of cardiovascular diseases (22).

Acknowledgement. This study was conducted as a part of project No.145010 financially supported by the Ministry for Science of the Republic of Serbia.

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Received: January 12, 2008

Accepted: January 28, 2008