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CRP levels are higher in patients with ST elevation than non-ST elevation acute coronary syndrome

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Short Running Title: CRP & acute coronary syndrome

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Abstract

Objective: There is intense interest in the use of C-reactive protein (CRP) for risk assessment. Therefore we aimed to study different high-sensitivity C-reactive protein (hsCRP) levels in acute coronary syndrome patients and to compare the difference between non-ST elevation myocardial infarction (NSTEMI) and ST myocardial infarction (STEMI) patients..

Methods: This is an observational study. Of the 89 patients recruited 60 patients had acute myocardial infarction (AMI). Three serial hsCRP levels at baseline on admission to hospital before 12 hours of onset of symptoms, peak levels at 36-48 hours and follow up levels after 4-6 weeks were analyzed and compared between non-ST elevation AMI and ST elevation AMI.

Results: STEMI patients had significantly higher BMI compared to NSTEMI patients. Creatine kinase myocardial bound (CKMB) and Aspartate aminotransferase (AST) were significantly higher in STEMI patients compared to NSTEMI patients ($p<0.05$**)**. CRP levels at baseline and at follow up did not differ significantly between the two groups ($p= 0.2152$, $p=0.4686$ respectively). There was a significant difference in peak CRP levels between the two groups. In STEMI patients it was significantly higher compared to NSTEMI patients ($p=0.0.0464$).

Conclusion: STEMI patients have significantly higher peak CRP levels compared to NSTEMI patients. These data suggest that inflammatory processes play an independent role in the pathogenesis of myocardial infarction. Thus, CRP may assist in risk stratification after myocardial infarction.

Key words: C-reactive protein, myocardial infarction, STEMI, NSTEMI, inflammation

INTRODUCTION

A large body of evidence suggests that inflammation plays a key role in the pathogenesis of atherosclerosis. The chronic inflammatory process can develop to an acute clinical event by the induction of plaque rupture leading to acute coronary syndromes [1]. More than 20 large prospective trials have shown that the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP) is an independent predictor of future cardiovascular events plus it predicts risk of incident hypertension and diabetes [2].

In acute coronary syndromes plaque rupture is induced by the inflammatory process in the atherosclerotic tissue. The pathogenesis of atherosclerosis is influenced by inflammatory mechanisms and different plasmatic markers of inflammation have been studied. CRP has been the most extensively studied. Initially it was suggested that CRP was a by-stander [3] marker of inflammation, but subsequent works demonstrated that it was a risk marker in both acute coronary syndromes (ACS) and in patients with myocardial ischemia [4,5].

CRP levels increase after acute myocardial infarction (AMI) but their changes in the process of an acute ischemic attack has been studied mainly in patients with non-ST elevation AMI [6, 7]. Therefore, it is interesting to discuss the value of follow-up measurements of hs-CRP in patients with coronary artery disease (CAD).

Therefore we aimed to study the differences in hsCRP levels in patients with two clinical forms of ACS of non-ST elevation myocardial infarction compared to ST myocardial infarction.

PATIENTS AND METHODS:

This prospective observational study was conducted at the department of Physiology and Cardiology of College of Medicine & King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia from August 2006 to December 2007. Consecutive eligible patients with either STEMI or NSTEMI who were admitted at King Khalid University Hospital were recruited. Of the 89 patients recruited 60 patients had evidence of AMI on the basis of the aforementioned criteria. The other 29 subjects were used as a control group. Of these, 11 manifested signs of unstable angina, 8 had chronic ischemic heart disease, and 10 had non ischemic diseases. The hs-CRP concentration of these patients with an acute coronary syndrome (ACS) was measured on admission to hospital before 12 hours of onset of symptoms, peak levels at 36-48 hours and follow up levels after 4-6 weeks.

This project was supported by College of Medicine Research Center (CMRC). The study protocol was approved by the Research Ethics Committee of CMRC. The individuals selected were informed about the details of the study and consent was obtained. Inclusion criteria included patients of any sex with both non-ST elevation acute coronary syndrome and ST elevation acute coronary syndrome. The diagnosis of myocardial infarction required the presence of at least 2 of these criteria (1) A history of characteristic prolonged (≥ 30 min) pain or discomfort (2) Creatine kinase (CK) elevation exceeding twice the upper limit of normal (or CK-MB ≥ 50% of total CK). Presence of new Q waves or new abnormal ST-T features [8].

Patients with STEMI were required to have: (1) continuous chest pain upon presentation, refractory to nitrates, and lasting ≥ 30 min; (2) ST-segment elevation of ≥ 0.2mV in ≥ 2 contiguous precordial leads, or ≥ 0.1mV in ≥ 2 contiguous limb leads, or new (or presumably new) left bundle branch block on admission electrocardiogram; (3) presentation in the first 12 h from index pain. Patients with NSTEMI were required to have angina like chest pain at rest in the last 24 h lasting ≥ 5 min, with associated ST-segment depression of ≥ 0.1mV in ≥ 2 contiguous leads upon presentation [9].

Patient with (1) angina of secondary etiology, (2) recent surgery, (3) active infection, or chronic inflammatory diseases (thyroid disorders, acute infections, stroke, diabetic ketoacidosis, non-ketotic hyperosmolar diabetes rheumatic diseases, chronic liver diseases, renal disorders, cancer and sepsis), (4) significant hepatic or renal dysfunction, and (5) malignancy, were not included (5) individuals with body temperature of >37.8℃ at admission (6) those who had suffered a coronary or cerebral event in that same period, those with complete left bundle block, those with pacemaker rhythm, and those with serious aortic valve disease, obstructive hypertrophic cardiomyopathy, and subjects who were critically ill or with ongoing or recent (< 1 month) infectious diseases (7) patients with surgical procedure in last 3 months were excluded. We followed the guidelines of the American Heart Association for measurement, evalauation and expression of hsCRP [10].

Fasting Venous blood samples were analyzed for Lipids comprising total cholesterol (TC), Triglycerides (TG), Low density Lipoprotein (LDL) and High density lipoprotein (HDL), Lipoprtein(a) [Lp(a)] and hsCRP. TC, TG, LDL and HDL were analyzed by enzymatic colorimetric method. The instrument used was autoanalyser Dimension (USA) and the kits were also provided by the same company. hsCRP and Lp(a) were measured by turbidimetric assay with commercial kits (Quantex Lp(a) supplied by BIOKIT, S.A., Barcelona, Spain) on a Hitachi 911, (ROCHE diagnostics, USA). The kit had a working range from 0.10 to 20.0 mg/L for hsCRP. One important attribute of C-reactive protein is its stability over time and the availability of automated assay techniques. Besides, the new assays are very sensitive and provide measurement of C-reactive protein at levels substantially below those levels measured by other traditional methods. For Lp(a) the Limit of Quantification (LOQ) was 1.3 mg/dL and the Limit of Detection (LOD) was 0.4 mg/dL.

The autoanalyser used was Hitachi 911, manufactured by ROCHE diagnostics, USA.

Statistical Analysis

The data was analyzed by computer software program Statistical Package for Social Sciences (SPSS version 10, Chicago). Descriptive characteristics and lipid profile of the study patients were calculated as Mean ± SD (Standard Deviation) or SEM (Standard error of mean) for continuous variables. To assess differences in Age, blood pressure, TC, LDL, HDL, TG and BMI the analysis of variance was utilized. hsCRP, Lp(a) and cardiac enzymes data, because of their extreme

skewness, was analyzed by non parametric statistical test Mann-Whitney U test and Wilcoxon (Kruskal–Wallis) test when comparing two or three groups, respectively. A p value of < 0.05 was considered as statistically significant.

RESULTS

Clinical characteristics, lipid profile, Lp(a) and hsCRP levels of STEMI and all NSTEMI patients are shown in table I. There were non significant differences between age and Blood pressure between Control and CAD subjects. TC and LDL levels did not differ significantly between the two groups. Lp(a) levels were significantly higher in both STEMI and NSTEMI patients compared to control subjects but among the two groups the difference was non significant.

STEMI patients had significantly higher BMI compared to NSTEMI patients. We also observed significantly higher levels of hsCRP in STEMI (1.59 ± 1.47) patients compared to NSTEMI (0.75 ± 0.99) patients ($p = 0.0472$).

Table II shows the diffrences in cardiac enzymes between the two groups. It was observed that Creatine kinase myocardial bound (CKMB) and Aspartate aminotransferase (AST) were significantly higher in STEMI patients compared to NSTEMI patients ($p<0.05$**)**.

CRP levels at baseline and at follow up did not differ significantly between the two groups ($p= 0.2152$, $p=0.4686$ respectively). There was a significant difference in peak CRP levels between the two groups. In STEMI patients it was significantly higher compared to NSTEMI patients ($p = 0.0464$) [Figure I].

Table I: Clinical characteristics of ACS patients with STEMI compared to NSTEMI.

	Control	NSTEMI	STEMI
N	**29**	**28**	**32**
Gender M/F	**18/11**	**21/7**	**22/10**
Age	**54.62 ± 10.60**	**59.22 ± 13.12**	**55.57 ± 11.44**
BMI	**26.12 ± 6.08**	**25.24 ± 7.44**	**29.23 ± 4.73****
BP Systolic	**129.93 ± 19.07**	**136.37 ± 23.68***	**130.41 ± 16.88**
BP Diastolic	**75.83 ± 12.26**	**79.56 ± 18.32**	**76.72 ± 11.84**
TC mmol/L	**4.38 ± 0.50**	**4.49 ± 1.66**	**4.22 ± 1.37**
TG mmol/L	**1.11 ± 0.49**	**2.02 ± 1.62**	**1.77 ± 0.84**
LDL mmol/L	**2.71 ± 0.53**	**2.72 ± 1.31**	**2.69 ± 1.03**
HDL mmol/L	**1.07 ± 0.32**	**0.69 ± 0.30**	**0.70 ± 0.20**
Lp(a) mg/dl	**14.57± 11.81##**	**31.92 ± 37.34**	**22.05 ± 18.66**

Systolic blood pressure (SBP), Diastolic Blood pressure (DBP), Total cholesterol (TC), Triglycerides (TG), Low density Lipoprotein (LDL) and High density lipoprotein (HDL) and Lipoprotein(a) [Lp(a)]. Differences were studied by Kruskal–Wallis -test for Lp(a) and ANOVA for other parameters.

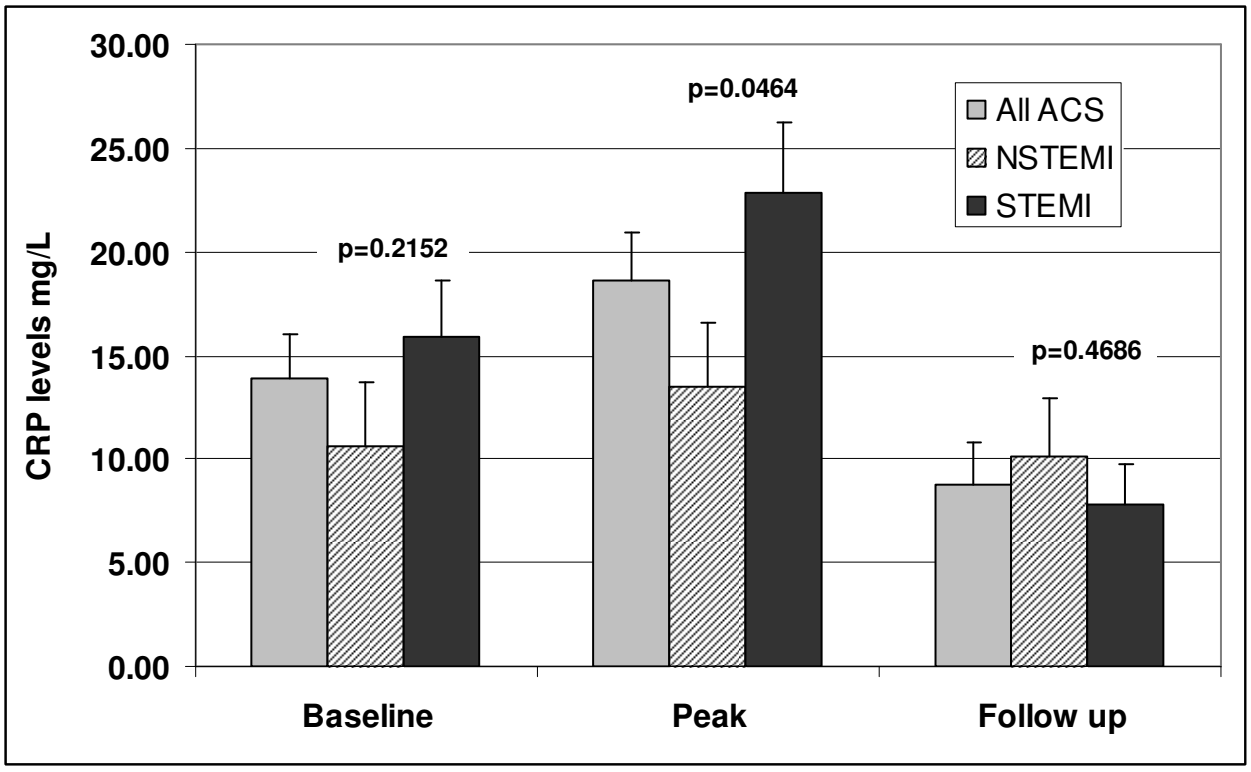
Data is expressed as Mean ± SD
*p<0.05 versus STEMI & Control
**p<0.01 versus NSTEMI & Control
p<0.01 versus NSTEMI & STEMI

Table II: Peak cardiac enzyme levels in ACS patients with STEMI compared to NSTEMI.

Cardiac Enzymes IU/L	**NSTEMI**	**STEMI**
Troponin T	**0.95 ± 1.51**	**2.61 ± 2.76**
CKMB	**111.75 ± 44.33**	**205.39 ± 152.15***
AST	**38.00 ± 31.13**	**95.00 ± 72.66***
LDH	**188.38 ± 92.63**	**309.00 ± 213.02**

Creatine kinase myocardial bound (CKMB), Aspartate aminotransferase (AST), Lactate dehydrogenase (LDH)
Differences were studied by Mann–Whitney -test
Data is expressed as Mean ± SD
*$p<0.05$ versus NSTEMI

Figure I: Comparison of mean CRP levels at baseline, peak and at 4-6 weeks of follow up in all ACS, NSTEMI and STEMI patients.



	Baseline	Peak	Follow up
All ACS	13.9	18.6	8.8
NSTEMI	10.6	13.5	10.1
STEMI	15.9	22.9	7.8

Differences were studied by Mann–Whitney -test

DISCUSSION

In patients with ACS, an increase in the CRP level at admission is associated with a poorer short term and long term prognosis. The majority of authors concur in that the admission CRP value reflects the baseline inflammatory status of the patient; thus, patients with ACS and high CRP levels at admission usually experience more important cardiovascular complications during follow-up [11].

A similarly designed study in ACS patients reported that although, CRP levels on admission were similar in all groups the pattern of CRP release and peak levels observed was clearly different in STEMI versus NSTEMI. Peak CRP level was 67 (36-112) mg/L in the STEMI group, 29 (20-87) mg/L in the NSTEMI group, and 18 (12-36) mg/L in the unstable angina group. In our study the difference in CRP levels was significant between STEMI and NSTEMI in the peak levels only, but the difference was non significant in the baseline and follow up readings. This suggests that it might be influenced by the degree of early myocardial tissue necrosis. Therefore, this variation in CRP kinetics should be taken into consideration when designing future studies [12].

Brunetti et al. reported that CRP plasmatic concentrations showed a different release curve in patients with Q-wave AMI in comparison with patients with non Q-wave AMI and with patients with UA. CRP peak concentrations did not correlate with ejection fraction and angiographic findings, but correlate with incidence of major adverse cardiac events. The higher increase in CRP levels during Q-wave MI than non Q-wave MI seems to be linked to the extension of myocardial damage rather than pre-existing inflammation [13].

The higher the maximum CRP recorded, the more serious is the infarction suffered, the greater the likelihood of ventricular remodeling, the lower the ejection fraction, and the greater the risk of heart failure, heart rupture, and death [14].

The results of the present study expand upon previous report that demonstrated non significant differences in CRP levels at baseline in patients with acute coronary syndromes and tended to be higher in successive samples [15].

Following AMI Fibrinogen, CRP, and IL-6 levels are reported to be significantly higher in patients with complications both as in-hospital and follow-up prognostic indicators [16, 17].

The level of C-reactive protein (CRP) can be used to identify patients with the most complicated coronary lesions and the greatest degree of intracoronary thrombosis, but can also help identify patients with apparently non-complex lesions that are susceptible to rupture—a problem that would lead to patient instability [18,19,20].

In a study by Jahn et al. most events in the observation period of 3 years occurred in patients with follow-up hs-CRP levels > 60% of the initial level. Therefore, it was hypothesized that a repeated measurement of hs-CRP levels in CAD patients could help to discriminate those at high risk of further events [21].

CRP measurement has a lot of advantages. Firstly it is a stable compound and secondly it can be measured at any time of the day without regards to biological clock. In contrast to results for cytokines such as IL-6, no circadian variation

appears to exist for hsCRP. Thus, clinical testing for hsCRP can be accomplished without regard for time of day [22].

There is an intracardiac inflammatory response in ACS that appears to be the result of evolution of myocardial necrosis as shown by higher CRP, TNFα, IL-6 and Troponin T in patients with major adverse cardiac events compared to those without MACE [23, 24] This suggests that the systemic inflammatory response may be the result of the evolution of myocardial infarction thus showing higher peak in transmural infarction.

Further studies are needed to elucidate the inflammatory process in ACS which may lead to novel therapeutic approaches and better application of currently available therapies. The present study could help us better understand the significance of CRP values, improve pharmacological therapies, and help improve the design of research projects examining the prognostic significance of CRP levels over the ACS spectrum.

Conclusion: Peak CRP levels are significantly higher in STEMI patients compared to NSTEMI patients. These data suggest that inflammatory processes play an independent role in the pathogenesis of myocardial infarction. Thus, CRP may assist in risk stratification after myocardial infarction.

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