ORIGINAL ARTICLE

Study of High Sensitive-CRP and Cardiac Marker Enzymes in Acute Coronary Syndrome

Srikrishna R[1], Ramesh S. T[2], Girishbabu R. J[3]*

[1]Department of Biochemistry, [2]Department of Pathology,[3]Department of Microbiology,

Sri Siddhartha Medical College, Agalakote, Tumkur-572107(Karnataka) India

Abstract:

Background: Inflammation has been proposed as a contributor to different stages in the pathogenesis of Coronary Heart Disease (CHD). High sensitive C-Reactive Protein (hs-CRP), an acute-phase plasma protein synthesized by the liver, is the most extensively studied systemic marker of inflammation. Elevated hs-CRP concentrations early in Acute Coronary Syndrome (ACS), prior to the tissue necrosis, may be a surrogate marker for cardiovascular co-morbidities. The cardiac marker enzymes Creatine Kinase myocardial bound (CK-MB), Aspartate Aminotransferase (AST) and lactate dehydrogenase (LDH) have been known to be increased in coronary artery diseases. *Objective:* The aim of the study was to measure hs-CRP levels and other cardiac marker enzymes in ACS patients and to compare the levels of hs-CRP with other cardiac marker enzymes between ST Elevation Myocardial Infarction (STEMI) and Non-ST Elevation Myocardial Infarction (NSTEMI) patients. *Material and Methods:* The study group consisted of 207 consecutive patients admitted to Sri Siddhartha Medical College Hospital within the first 6 hours from the onset of chest pain. Patients were diagnosed as Unstable Angina (UA), (n=84); STEMI (n=63) and NSTEMI (n=60). ACS patients were compared with 211 healthy age and sex matched controls. Hs-CRP**,** CK-MB, AST and LDH levels were measured by standard methods in both groups at baseline and for cases at 36-48 hours i.e. Peak levels. *Results:* ACS patients had significantly (p<0.05) higher levels of hs-CRP, CKMB, AST and LDH in comparison to controls at baseline. Hs-CRP, CK-MB, AST and LDH levels were significantly higher in STEMI patients compared to NSTEMI patients (p<0.05) at baseline**.** There was a significant difference regarding peak hs-CRP levels between the two groups, as STEMI patients had significantly higher peak hs-CRP levels compared to NSTEMI patients (p<0.05). *Conclusion:* STEMI patients have significantly higher peak hs-CRP levels compared to NSTEMI patients. These data suggest that inflammatory processes play an independent role in the pathogenesis of myocardial infarction. Thus, Hs-CRP assessment may assist in risk stratification after myocardial infarction.

Keywords: C-reactive protein; acute myocardial infarction; acute coronary syndrome; inflammation.

Introduction:

Acute coronary syndrome (ACS) which is a collective term for Unstable Angina (UA), ST Elevation Myocardial Ischemia (STEMI) and Non-ST Elevation Myocardial Ischemia (NSTEMI) [1] is a major cause of mortality and morbidity in both developed and developing countries including India. Inflammation has been proposed as a contributor to different stages in the

pathogenesis of Coronary Heart Disease (CHD), including the lifelong process of atherogenesis, the acute atherothrombotic event that causes ischemic necrosis in acute myocardial infarction, and the myocardial damage after ischemia [2].

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

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. It is interesting to discuss follow-up measurements of hs-CRP in patients with coronary artery disease (CAD). Hence, we aimed to study the differences in hs-CRP levels in patients with two clinical forms of ACS of STEMI compared to NSTEMI.

Materials and Methods:

The present study was done at Sri Siddhartha Medical College Hospital and Research Centre. The 207 consecutive patients admitted to the intensive coronary care unit within 6 hours after the onset of chest pain and other symptoms were included in this study. The study duration was from February 2013 to July 2014.

Based on clinical history, the results of ECG, plasma cardiac markers, and stress test testing, patients were diagnosed by physicians as UA (n=84), STEMI (n=63) and NSTEMI (n=60). The study also included 211 age and sex matched controls selected from persons attending the outpatient department and admitted for other illnesses without coronary artery disease which was assessed by history and clinical examination. The study was approved by the Ethics Committee of the college and informed consent was taken from each patient.

Patient with angina of secondary etiology, recent surgery, 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, significant hepatic or renal dysfunction, individuals with body temperature of >37.8°C at admission, those who had suffered a coronary or cerebral event at the time of admission, those with serious aortic valve disease, obstructive hypertrophic cardiomyopathy, were excluded from the study.

In both, cases and controls, at baseline i.e. immediately after admission, 7ml of venous blood was drawn under aseptic conditions and serum was separated for analysis of hs-CRP, CK-MB, AST and LDH. In cases another sample of blood was drawn at 48 hrs after admission and serum was analysed for hs-CRP, CK-MB, AST and LDH. Hs-CRP levels were measured by

immuno-turbidimetric method, CK-MB levels by enzymatic method, lipid profile by enzymatic method and AST by IFCC method using ERBA Chem 7 semi-automated analyzer using ERBA reagents. Fasting samples were used for measuring lipid profile.

Statistical Analysis:

Statistical analysis was done by students 't' test with p value less than 0.05 considered as significant using SPSS version 14.

Results:

Table 1: Clinical Characteristics of Controls and Cases

Groups	Controls (n=211)	Cases (ACS)		
		Unstable Angina (n=84)	ST Elevation Myocardial Ischemia (n=63)	Non-ST Elevation Myocardial Ischemia (n =60)
Age (yrs)	45±10.39	40±19.54	41±16.43	43±13.45
Sex M/F	109/102	44/39	35/28	34/26
TC (mg/dl)	137±34.68	209±38.23	239± 44.77	213±32.97
TG(mg/dl)	108±54.86	195±54.34	217±62.32	199±46.54
HDL(mg/dl)	43.6±16.44	37.4±17.14	30±11.56	36±8.71
LDL(mg/dl)	87±45.23	169±49.54	179±65.66	165±54.76
Systolic BP (mmHg)	129.93±19.06	134.32±27.56	146.37±32.84	131.41±29.88
Diastolic BP (mmHg)	75.83±12.26	85.24±23.89	88.56±27.32	84.72±21.66

TC= Total cholesterol, TG=Triglycerides

Table 2: Comparison of hs-CRP and Cardiac Enzyme Levels between Controls and Cases at Baseline

Parameter	Controls (n=211)	Cases (n=207)			P value
		Unstable Angina (n=84)	ST Elevation Myocardial Ischemia (n =63)	Non ST Elevation Myocardial Ischemia (n =60)	
hs-CRP mg/L	0.70±0.67	4.30 ± 0.57	7.20±0.83	5.23±0.84	0.00
CK-MB IU/L	6.46±2.00	55.12±11.96	85.66±20.48	63.29±10.86	0.00
AST IU/L	16.01±4.55	21.29 ± 9.76	30.60±10.04	26.91±11.64	0.02
LDH IU/L	153.36±22.58	155.91±26.97	163.80±33.38	161.53±43.37	0.17

*p < 0.05 is considered as significant.

Table 3: Comparison of Peak hs-CRP Levels and Peak Cardiac Enzyme Activity Levels between STEMI and NSTEMI Cases

Parameters	ST Elevation Myocardial Ischemia (n=63)	Non ST Elevation Myocardial Ischemia (n=60)	P value
hs-CRP (mg/L)	12.59 ± 2.74	7.49 ± 2.98	0.00
CK-MB (IU/L)	145.39 ± 35.15	115.30 ± 19.59	0.00
AST (IU/L)	147.50 ± 38.97	81.33 ± 26.13	0.00
LDH (IU/L)	356.63 ± 35.96	314.32 ± 33.87	0.00

*p < 0.05 is considered as significant.

Table 1 shows clinical characteristics, blood pressure and lipid profile of controls and cases. The mean age in the control group was 45±10.39 years and in the patient group 40±19.54 yrs, 41±16.43 yrs and 43±13.45 yrs for UA, STEMI and NSTEMI respectively. Total cholesterol, triacyl glycerol, LDL and blood pressure levels were significantly higher in ACS patients compared to controls (p < 0.005). HDL cholesterol levels were significantly lower in cases compared to control (p<0.005).

Table 2 shows the comparison of hs-CRP levels and other cardiac enzyme activity levels between controls and ACS cases at the baseline. The mean levels of hs-CRP (p<0.05), CK-MB (p<0.05) and AST (p=0.02) were significantly higher in cases when compared to controls at the baseline. There was no significant difference in the mean levels of

LDH between cases and controls at the baseline p=0.17 (p < 0.05). Amongst the cases, highest mean levels of hs-CRP, CK-MB and LDH were found in STEMI patients compared to other two groups. Mean AST levels were highest in UA case compared to other groups.

The comparison of mean levels of hs-CRP, CK-MB, AST and LDH between STEMI and NSTEMI cases at the peak i.e. at 48 hrs after admission are shown in Table 3.

The mean levels of hs-CRP, CK-MB, AST and LDH were significantly (p<0.005) higher in STEMI cases compared to NSTEMI cases at the peak. ANOVA method was used to compare the data between the two groups.

Discussion:

CRP, named for its capacity to precipitate the somatic C-polysaccharide of *Streptococcus pneumoniae,* was the first acute phase protein to be described and it is an exquisitely sensitive systemic marker of inflammation and tissue damage. The presence of CRP within most atherosclerotic plaques and all acute myocardial infarction lesions, coupled with binding of CRP to lipoproteins and its capacity for pro-inflammatory complement activation, suggests that CRP may contribute to the pathogenesis and complications of cardiovascular disease [3].

In the present study, baseline hs-CRP along with classical cardiac markers such as CK-MB and AST are increased in ACS compared to controls. This increase is statistically significant which reflects the baseline inflammatory status of the patient.

In patients with ACS, persistent or worsening of symptoms and signs of ischemia despite full medical therapy indicate a poor prognosis. A role for inflammation in UA is evidenced by systemic release of thromboxanes and leukotrienes, and the presence of activated circulating leukocytes in several studies [4, 5].

Dyslipidemia (Increased total cholesterol, triglycerides & LDL along with decreased HDL) is evident in this study (Table 1). Dyslipidemia along with chronic inflammatory process plays an important role in the formation of atheromatous lesions, causing stenosis or occlusion of arterial lumens. Chronic inflammatory markers such as cytokines and adhesion molecules, pose the risk of CVDs as evident in various studies among which hs-CRP is demonstrated to be the most consistent predictor of future CVDs in association with many traditional risk factors of CVDs [6-8]. In this study, pattern of increase of inflammatory & classical cardiovascular risk markers is as follows: hs-CRP & CK-MB: STEMI > NSTEMI > UA, AST: UA > STEMI > NSTEMI, LDH: STEMI > UA > NSTEMI.

Elevated hs-CRP levels during Q-wave MI than in non Q-wave MI seems to be linked to the extension of myocardial damage, rather than to the pre-existing inflammation. The intracardiac inflammatory response in ACS can be attributed to the evolution of myocardial necrosis indicated by higher hs-CRP, TNFα, IL-6 and troponin T levels in patients with major adverse cardiac events. Severe myocardial infarction causes

greater ventricular remodelling & lowers ejection fraction worsening the cardiac failure [9-12]. Tissue necrosis is a potent acute-phase stimulus, and following myocardial infarction, there is a major CRP response, the magnitude of which reflects the extent of myocardial necrosis. Furthermore, the peak Hs-CRP values at around 48 hours after the onset, powerfully predict outcome after myocardial infarction. Importantly, hs-CRP is deposited within all acute myocardial infarcts, and experimental evidence through rat heart models shows that the hs-CRP response not only reflects tissue damage in this context, but may also contribute significantly to the severity of ischemic myocardial injury [13- 15]. These studies substantiate our reporting of peak levels of mean hs-CRP in STEMI patients at 48 hours. Our results are in agreement with that of the studies carried out by Krintus *et.al* [16] and Sheikh *et. al* [17].

Limitations:

There is no correlation of hs-CRP & classical cardiac markers with ejection fraction & angiographic findings. Other inflammatory markers associated with adverse cardiac events are not studied concurrently. The small number of subjects studied may not reflect the entire population. However, further extensive studies may elucidate the inflammatory process in ACS, may aid in novel therapeutic approaches & better management of ACS patients which might decrease the morbidity & mortality associated with CVDs.

Conclusion:

The present study says that estimation of Hs-CRP levels at 6 hours and 48 hours after the onset of symptoms in ACS patients can help us in better understanding its prognostic value (3.0 mg/L) and risk stratification of the cases which may help in optimizing the therapeutic approaches to manage ACS patients.

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*Author for Correspondence: Dr. Srikrishna R. Associate Professor, Department of Biochemistry, Sri Siddhartha Medical College, Agalakote, Tumkur-572107Karnataka, India Cell: 9844428095 Email: docsrikrishna@rediffmail.com