Association between increase level of high-sensitive CRP (hs CRP) and non-arrhythmic ECG changes and echocardiographic abnormalities in patients with acute coronary syndrome

asghar rahmani[1], roholla hemmati[1], and Seyed Hossein Kia[1]

[1]Affiliation not available

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Abstract

Background: As elevation of serum C-reactive protein (CRP) is occurred following left ventricular dysfunction (LVD), relationship between increasing serum CRP level and abnormal changes in electrocardiography(ECG) pattern. The present study aimed to examine association between increase level of high-sensitive CRP (hs-CRP) and non-arrhythmic ECG changes and echocardiographic abnormalities in patients with acute coronary syndrome (ACS). Methods: This cross-sectional study was conducted on 120 consecutive patients finally diagnosed as ACS and hospitalized at cardiac care units (CCU). The participants were classified as the two groups with increased level or normal of hs-CRP level. Results: The patients with the increased level of hs-CRP had significantly higher level of cardiac enzymes. The group with increased level of hs-CRP experienced more ST-segment elevation myocardial infarction (STEMI) than those with normal serum hs-CRP level, but other diagnoses including unstable angina, non-STEMI, heart failure, and emergency hypertension were similarly observed in both groups. The two groups were comparable in terms of mean left ventricular ejection fraction (LVEF), left ventricular end diastolic diameter (LVeDD), prevalence of valvular heart diseases as well as in wall motion abnormality assessed by echocardiography. ST-segment elevation in different leads was more frequent in those with elevated hs-CRP level than in the group with normal hs-CRP condition (19.6% versus 1.4%, p = 0.001); but ST-segment depression and T wave inversion were similarly revealed in the two groups. Conclusion: Elevated level of hs-CRP can predict occurrence of STEMI, but may not be valuable to predict echocardiographic abnormalities including LVD or hypertrophy.

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Key words: CRP, acute coronary syndrome, ECG, myocardial infarction

Running title: CRP changes in patients with acute coronary syndrome

INTRODUCTION

CRP as an acute-phase reactant protein normally circulates at non-sensed low level in the serum, however in some conditions including acute inflammatory processes, tissue injuries, or acute infections, its producing in hepatic cells and rising in circulation can be markedly induced [1,2]. In this regard, it has been a growing interest in the use of this marker as a sensitive marker for predicting and following progression of each clinical conditions underlined by inflammatory or infectious processes [3-5]. As recently revealed, different abnormal cardiac conditions such as coronary atherosclerosis, ventricular hypertrophy and other ventricular filling abnormalities, heart failure, and even valvular heart diseases has an underlying inflammatory etiologies accompanied by increased level of inflammatory responses and thus CRP may have a major role to predict various types of cardiovascular diseases even in apparently healthy subjects [6,7]. This hypothesis has been strengthened by recent histological studies discovering activated circulating leucocytes, evidence of systemic release of thromboxanes, and other inflammatory mediators besides elevated level of CRP in these abnormal cardiovascular conditions [8,9].

Furthermore, the significant association between elevation level of CRP with reduced left ventricular systolic and diastolic dysfunction as well as abnormality in long-term left ventricular remodeling has been well recognized [10,11]. Because of the presence of close association between ventricular systolic and diastolic dysfunction and abnormal changes in electrocardiographic and echocardiographic patterns, it has been recently hypothesized that as elevation of serum CRP is occurred following LVD, relationship between increasing serum CRP level and abnormal changes in electrocardiography pattern can be expected. Hence, the present study aimed to assess association between increase level of hs-CRP and non-arrhythmic ECG changes and echocardiographic abnormalities in patients with acute coronary syndrome.

METHODS

This cross-sectional study was conducted on 120 consecutive patients finally diagnosed as acute coronary syndrome and hospitalized at CCU wards of Mostafa Khomeini hospital in Ilam(Iran) in 2018-2019. The diagnosis of acute coronary syndrome based on clinical manifestation, rising cardiac enzymes, and electrocardiographic ischemic changes so acute was defined by a positive troponin blood test in the setting of symptoms of angina or an anginal equivalent and/or electrocardiographic changes consistent with an MI (evolutionary ST-T changes or a new Q wave) [12]. Also, patients were diagnosed with unstable angina if they had a negative troponin blood test and any one of the following: new onset angina of at least Canadian Cardiovascular Society Classification class III, rest angina, recent worsening of angina, or angina that occurred within myocardial infarction 2 weeks of an myocardial infarction [13].

Baseline characteristics of the participants including demographics, medical history, history of medications, and the level of cardiac enzymes were collected by interviewing on admission or reviewing hospital recorded charts. On admission, the level of HS-CRP was measured using a commercial kit in all participants. The participants were classified as the two groups with increased level of HS-CRP ($>$ 1 mg/dl) as the case group and with normal HS-CRP level ([?] 1 mg/dl) as the control group. The patients in both groups were monitored during CCU hospitalization and any abnormal non-arrhythmic changes in ECGs were recorded at study checklist. Also, the levels of lipid profile were also measured in all subjects.

Results were presented as mean $\pm$ standard deviation (SD) for quantitative variables and were summarized by

frequency (percentage) for categorical variables. Continuous variables were compared using t test or Mann-Whitney U test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups. Categorical variables were, on the other hand, compared using chi-square test. For the statistical analysis, the statistical software SPSS version 20.0 for windows (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

RESULTS

Among 120 patients suffered acute coronary syndrome, 46 (38.3%) faced with increased level of hs-CRP. Table 1 compares baseline characteristics between the two groups with normal and elevated level of hs-CRP. The two groups were similar in gender and age distribution, prevalence of cardiovascular risk factors including obesity, diabetes mellitus, hyperlipidemia, and hypertension, clinical manifestations, vital signs, as well as oral medications. Regarding laboratory parameters, increased level of hs-CRP was accompanied with raised levels of fasting blood sugar, triglyceride, and liver enzymes in serum. With respect to the difference in cardiac condition, those with the increased level of hs-CRP had significantly higher level of cardiac enzymes including lactate dehydrogenase (LDH), creatine kinase MB (CKMB), troponin I, and also N-acetyl cysteine (NAC) when compared with normal serum hs-CRP status (table 2). Regarding underlying cardiovascular abnormalities, the group with increased level of hs-CRP experienced more ST-segment elevation myocardial infarction (STEMI) than those with normal serum hs-CRP level, but other diagnoses including unstable angina, non-STEMI, heart failure, and emergency hypertension were similarly observed in both groups. With regard to the difference in echocardiographic parameters, the two groups with increased and normal serum hs-CRP level were comparable in terms of mean left ventricular ejection fraction (LVEF), left ventricular end diastolic diameter (LVeDD), prevalence of valvular heart diseases such as aortic insufficiency, mitral regurgitation, and tricuspid regurgitation, as well as in left ventricular hypertrophy. Also, there was no difference in regional wall motion abnormality between the two groups (table 2).

With regard to common non-arrhythmic ECG abnormalities (table 3), ST-segment elevation in different leads was more frequent in those with elevated hs-CRP level than in the group with normal hs-CRP condition (19.6% versus 1.4%, $p = 0.001$); but ST-segment depression was similarly revealed in the two groups (36.5% versus 41.3%, $p = 0.598$). In group with increased level of hs-CRP, ST changes was occurred in precordial leads in 37.0%, in limbs leads in 13.0%, and in both types of leads in 8.7%; while these frequencies in another group were 18.9%, 8.1%, and 10.8%, respectively with no difference (table 3). The frequency of inverted T wave in the two groups was 37.0% and 29.7%, respectively with no difference ($p = 0.411$).

DISCUSSION

Our study demonstrated a similar abnormal changed in echocardiography parameters between the groups with and without serum hs-CRP elevation regarding left ventricular dysfunction, left ventricular hypertrophy and wall motion abnormality, however with respect to non-arrhythmic ECG changes, ST segment elevation indicating STEMI was more frequent in those with increased level of hs-CRP. On the other hand, elevation level of hs-CRP could effectively predict occurrence of STEMI and thus elevated level of hs-CRP may have a major role in pathophysiological basis of STEMI. However, elevation of this biomarker may not have central role in occurring other non-arrhythmic ECG changes. Similar finding was found in a study by Adler et al. that showed a significant association between high CRP levels on the second and third day following first AMI and ST elevation in ECG pattern [14]. In contrast, Okin et al. demonstrated only a weak correlation between CRP and ECG ST depression pattern [15]. In a population-based study of 8,076 subjects, Asselbergs et al. showed that although ST-segment and T-wave abnormalities were modest univariate correlates of an increased CRP, only Q-wave myocardial infarction remained associated with increased CRP levels after adjusting for standard cardiovascular risk factors [16]. In fact, in our study, although increased level of hs-CRP could effectively predict STEMI, however we could not reveal association between elevated level of this marker and left ventricular dysfunction assessed by echocardiography. On the other hand, early increased level of hs-CRP may predict early ischemic events such as STEMI; however occurrence of left ventricular dysfunction or other echocardiographic events may need to more time. So, it has been shown that even a mild elevation of the CRP level in STEMI patients may be associated with worsening of diastolic function and elevated left ventricular

filling pressure, independent of left ventricular systolic function or cardiac out-put. Previous studies have demonstrated the relation of early CRP elevation with left ventricular systolic function, future heart failure, and mortality in MI patients [17–21]. Besides, our study finding on insignificant association between elevated level of hs-CRP and echocardiographic indices such as left ventricular dysfunction and hypertrophy may be affected by considering a narrow range of hs-CRP measurements in our study population ranged less than 10, so considering a wide range of CRP may reveal positive association between elevation of hs-CRP level and left ventricular dysfunction and hypertrophy in echocardiography.

For explaining pathophysiological fundaments of inducing STEMI following elevation of hs-CRP, it has been shown that myocardial infarction size following acute coronary occlusion can be determined by complement mediated inflammation, and that human CRP, indicated in both human and animal studies, can be responsible for some of this complement activation [22]. Some other mechanisms revealed for this event include increasing phosphatidylinositol3-kinase activity, upregulating inducible nitric oxide synthase, certain cell signal transduction pathways including the mitogen-activated protein kinase pathway, and nuclear factor ϰ-B, upregulating angiotensin II type 1 receptor in vascular smooth muscle cells, and directly quenching the production of nitric oxide by endothelial cells, resulting in increased production of endothelin-1, and elevation of von Willebrand factor, which is known to be associated with endothelial dysfunction [23-27].

In conclusion, elevated level of serum hs-CRP can effectively predict occurrence of STEMI in patients with acute coronary syndrome. The present study could not demonstrate predictive role of this biomarker for abnormal echocardiographic changes including left ventricular hypertrophy or dysfunction as well as abnormal regional wall motion abnormality probably due to considering a narrow range of hs-CRP (less than 10) or employing a small sample size.

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Table 1: Comparing baseline characteristics between the study groups

Item	Normal HS-CRP Group (n = 74)	Increased HS-CRP group (n = 46)	P-value
Male gender	28 (37.8)	24 (52.2)	0.123
Age, year	59.56 ± 12.52	60.89 ± 14.42	0.596
BMI, kg/m2	28.78 ± 4.66	30.72 ± 23.60	0.493
Married status	74 (100)	43 (93.5)	0.054
Urban residence	55 (74.3)	35 (76.1)	0.828
History of smoking	6 (8.1)	2 (4.3)	0.422
History of diabetes	15 (20.3)	16 (34.8)	0.077
History of hypertension	35 (47.3)	22 (47.8)	0.955
Manifestations			
Chest pain	3 (4.1)	0 (0.0)	0.565
Palpitation	1 (1.4)	0 (0.0)	0.889
Dyspnea	1 (1.4)	0 (0.0)	0.889
Medication			
TCA	1 (1.4)	2 (4.3)	0.733
ACE-inhibitor	1 (1.4)	1 (2.2)	0.737
Thiazides	1 (1.4)	1 (2.2)	0.737
Statins	1 (1.4)	1 (2.2)	0.737
Aspirin	4 (5.5)	0 (0.0)	0.442
Beta-blockers	1 (1.4)	2 (4.3)	0.733
Vital signs			
Heart rate, /min	78.50 ± 15.76	78.57 ± 13.50	0.981
SBP, mmHg	119.42 ± 26.65	125.72 ± 27.28	0.215
DBP, mmHg	77.43 ± 13.11	79.17 ± 13.81	0.490
Laboratory markers			
HDL, mg/dl	57.23 ± 10.98	57.24 ± 15.77	0.997
LDL, mg/dl	105.85 ± 45.21	100.50 ± 27.60	0.472
Triglyceride, mg/dl	122.64 ± 56.85	161.91 ± 88.93	0.004
Total cholesterol, mg/dl	162.54 ± 34.01	172.57 ± 52.04	0.250
SGOT, mg/dl	18.53 ± 16.73	80.96 ± 124.17	< 0.001
SGPT, mg/dl	20.00 ± 14.47	37.54 ± 37.27	< 0.001
FBS, mg/dl	126.59 ± 63.10	154.15 ± 85.70	0.046

Table 2: Results of cardiac assessment in the study groups

Item	Normal HS-CRP Group (n = 74)	Increased HS-CRP group (n = 46)	P- Value
Cardiac enzymes and biomarkers			
Mean LDH level	4.44 ± 3.32	7.33 ± 6.26	0.001

Item	Normal HS-CRP Group (n = 74)	Increased HS-CRP group (n = 46)	P- Value
Mean CKMB level	31.19 ± 55.69	91.96 ± 118.96	< 0.001
mean troponin I level	1.03 ± 0.26	1.21 ± 0.41	0.012
Mean NAC level	1.42 ± 0.25	6.47 ± 1.05	< 0.001
ACS diagnosis			
Unstable angina	47 (63.5)	20 (43.5)	0.244
Emergency hypertension	1 (1.4)	1 (2.2)	0.737
Heart failure	3 (4.1)	1 (2.2)	0.589
STEMI	1 (1.4)	5 (10.9)	0.039
NSTEMI	2 (2.7)	1 (2.2)	0.860
LV dysfunction	0 (0.0)	1 (2.2)	0.388
Echocardiography indices			
LVEF, %	28.64 ± 24.03	26.50 ± 21.51	0.623
LVeDD	2.11 ± 0.94	2.13 ± 0.75	0.886
AI	9 (12.2)	1 (2.2)	0.087
TR	6 (8.1)	4 (8.7)	0.728
MR	10 (13.5)	5 (10.9)	0.660
RWMA	3 (4.3)	4 (9.8)	0.469
LVH	5 (6.8)	4 (8.7)	0.695

Table 3: Cardiac arrhythmias in the two study groups

Item	Normal HS-CRP Group (n = 74)	Increased HS-CRP group (n = 46)	P –value
Type of ST change			
ST segment elevation	1 (1.4)	9 (19.6)	0.001
ST segment depression	27 (36.5)	19 (41.3)	0.598
Location of ST change			
Precordial leads	14 (18.9)	17 (37.0)	0.097
Limbs leads	6 (8.1)	6 (13.0)	0.430
Both	8 (10.8)	4 (8.7)	0.999
T wave changes			
T wave inversion	22 (29.7)	17 (37.0)	0.411
T wave tall	1 (1.4)	0 (0.0)	0.999