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ORIGINAL ARTICLE

Role of High Sensitivity C-Reactive Protein in The Prediction of Future Cardiovascular Events in Patients Presenting with Acute Coronary Syndromes

Sameh Salama, MD[1]; Ahmed El-Damaty, MD[1]; Sherif El-Tobgi, MD[1]; Amani El-Kholy, MD[2] and Mervat Gaber, MD[2]

[1]Cardiology and [2]Clinical Pathology Departments, Cairo University, Cairo, Egypt.

Background Inflammation appears to be pivotal in all phases of atherosclerosis. An important marker of inflammation is C-reactive protein (CRP).

Objective We thought to test the hypothesis that high sensitivity CRP (Hs-CRP) measured at admission with acute coronary syndromes (ACS) and at regular follow up durations is predictive of future cardiovascular events (CVE) and to assess its relation to the complexity of coronary stenoses and to the coronary score as a surrogate of the total atherosclerotic burden.

Methods We prospectively enrolled 91 patients presenting with ACS. Clinical examination excluded those with evidence of infection or inflammation. All patients underwent coronary angiography. Serum samples for measuring Hs-CRP level were withdrawn then patients were followed at 1, 4, 8 and 12 months and assessed for the occurrence of composite end point of nonfatal MI, unstable angina or cardiac death. Samples for Hs-CRP were withdrawn in the 1st three follow up visits.

Results Admission Hs-CRP level could not predict future CVE (P= 0.9) and did not correlate with complexity of coronary stenoses (P= 0.42), meanwhile Hs-CRP at all follow up visits predicted future CVE (P= 0.001, 0.004 and 0.01 respectively) and correlated with lesion complexity (P= 0.001, 0.01 and <0.001respectively). Hs-CRP that preceded the event "pre-event CRP" was significantly higher than samples not followed by events. A cutoff value of 7.3mg/l or a 4.3 fold rise in CRP level had the highest sensitivity and specificity in predicting events. Despite being higher in patients developing events, coronary score did not correlate with any of the CRP samples.

Conclusions Hs-CRP, done at admission could be useful in following patients after ACS and predicting the occurrence of future events. Its rise prior to the event indicates that Hs-CRP may not be just a mere marker of plaque instability, but rather a mediator of atherosclerosis through its pro-inflammatory and pro-atherogenic effects.

Keywords High sensitivity CRP, Coronary atherosclerosis, Acute coronary syndromes.
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INTRODUCTION

Recent advances in basic sciences have established a fundamental role of inflammation in mediating all stages of atherosclerosis including plaque rupture and overlying thrombosis, a process that involves cytokines and other bioactive molecules and cells that are characteristic of inflammation e.g. (macrophages and T-lymphocytes) (1). Accordingly, several inflammatory markers have been studied as a mean to assess the ongoing inflammatory process of atherosclerosis. Among these markers, high sensitivity CRP (Hs-CRP) has been considered the analyte of choice, after consideration of the various analytes stabilities, assay precision, accuracy and availability and the presence of standards for proper assay calibration (2).

A number of studies examined whether increased levels of CRP on admission with a documented myocardial infarction (MI) or in patients with unstable angina could predict future cardiovascular events, but data are still controversial. In the present study, we thought to test the

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Abbreviations and Acronyms	
HS-CRP	: High Sensitivity C Reactive Protein
ACS	: Acute Coronary Syndromes
CVE	: Cardiovascular Events
QCA	: Quantitative Coronary Analysis
ANOVA	: Analysis of Variance
LDL-C	: Low Density Lipoprotein Cholesterol

hypothesis that high sensitivity CRP measured at admission with ACS and at regular follow up durations is predictive of future cardiovascular events and to assess the relation of CRP levels to the complexity of coronary stenoses and to the coronary score as a surrogate of the total atherosclerotic burden.

MATERIAL

Patients

Ninety-one patients presenting with ACS were enrolled prospectively. ACS was defined as prolonged (>20 minutes) ischemic chest pain in the preceding 24 hours associated with transient or persistent ischemic ECG changes with or without raised levels of serum markers of myocardial damage (3).

Patients with life threatening arrhythmias, cardiogenic shock, advanced cardiac valvular lesions, cardiomyopathy, infections; inflammatory diseases and advanced terminal illness (renal, hepatic or malignancy) were excluded from the study.

Methods

On admission, all patients included in the study were subjected to detailed history taking, complete clinical cardiac examination together with screening for any clinical evidence of active infection or inflammation, that would exclude the patient from the study cohort. Twelve-lead surface electrocardiogram, trans-thoracic echocardiography for estimation of the ejection fraction using modified Simpson's method and coronary angiogram was performed to all patients. The following Laboratory work up performed: fasting blood sugar, serum creatinine, electrolytes, cardiac enzymes, 12-hours fasting lipid profile (total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides) and a serum sample for Hs-CRP level that was withdrawn, centrifuged and the separated serum was stored at -700C.

Angiographic Analysis

Coronary arteriogram was performed at the index admission and revascularization procedures performed as indicated. Qualitative angiographic data analysis included the segment of the vessel involved and the type of the lesion (A, B or C) (4), quantitative angiographic analysis (QCA) included lesion length, reference lumen diameter, minimal lumen diameter and percent diameter stenosis.

The total atherosclerotic burden was quantified using a coronary score that represents the sum of (percent stenosis score times extent score) over 15 coronary segments where percent stenosis was given a score of 1, 2 and 3 when the reduction in the vessel diameter was <10 percent, 10-25 percent and >25 percent respectively. The extent of the plaque was given a score of 0, 1, 2 and 3 when the vessel was normal, containing 1 or 2 plaque, more than 2 plaques with intervening normal vessel segment and more than 2 plaques producing continuous vessel wall irregularities respectively (5, 6).

Follow Up and Study Endpoints

All patients were followed up for a period of one year. Visits were scheduled at one, four, eight and twelve months, during which patients were subjected to detailed history taking for the recurrence of any anginal attacks, complete clinical examination with screening for any clinical evidence of active infection or inflammation, twelve-lead surface ECG was obtained for comparison with the ECG obtained on hospital discharge, and serum samples were withdrawn for Hs-CRP estimation during the first three visits at one, four and eight months. Non-fatal acute MI, unstable angina requiring hospitalization, treatment and/or urgent revascularization and cardiac death were considered the primary endpoints of the study.

High Sensitivity CRP Measurement

At the end of the follow up duration of all patients, Hs-CRP levels at the index admission, follow up at one, four and eight months were quantified using the high sensitivity CRP-ELISA assay (method according to the manufacturer) and termed CRP0, CRP1, CRP2 and CRP3 respectively.

Statistic

Data were statistically described in terms of range, mean±standard deviation (±SD), frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables between events groups was done using Student t test for independent samples in comparing 2 groups when normally distributed and Mann Whitney U test for independent samples when not normally distributed.

Comparison of CRP between the different types of events was done using Kruskal-Wallis analysis of variance (ANOVA) test. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5.

Accuracy was represented using the terms sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy, the likelihood ratio of a positive test and the likelihood ratio of a negative test. Receiver operator characteristic (ROC) analysis was used to determine the optimum cut off value for the studied diagnostic markers.

RESULTS

Population Characteristics

Baseline characteristics of the study population are shown in (Table 1). About 70% of the study populations were males, 49.5% were hypertensive and 42.3% were diabetic indicating a high risk group. Those who performed prior revascularization either PCI or CABG represented 13.3% of the study population.

Table 1: Baseline characteristics of 91 patients presenting with acute coronary syndromes:

Demographic data	Number	Percent (%)
Male gender	63	69.2
Smoking	55	60.4
Obesity	40	44
Diabetes Mellitus	39	42.9
Hypertension	45	49.5
Family H/O CAD	12	13.2
Prior Revascularization		
PCI	11	12.1
CABG	2	2.2
Both	1	1.1

PCI= Percutaneous Coronary Intervention, *CABG*= Coronary Artery Bypass Grafting; categorical variables are expressed as (number) and percent.

Relation Between Baseline Characteristics and the Study Primary Endpoints

Thirty-five patients (38.5%) reached one of the study endpoints (eventful group) while 56(61.5%) patients did not (uneventful group). Diabetes mellitus and hypertension were predictive of the occurrence of the study endpoints (P <0.001 for both risk factors). Patients who reached one of the study endpoints were older (57+/-8.6 vs. 53.6+/-8.9 in the eventful vs. uneventful group respectively, p= 0.04). Sex differences, smoking, obesity and family history of coronary artery disease showed no statistically significant difference between the eventful and the uneventful groups (P values were 0.35, 0.34, 0.11 and 0.69 respectively). Total cholesterol, LDL cholesterol and total leucocytic count showed a statistically significant increase in the eventful group (233+/-54,155+/-25 and 10.7+/-3.5 respectively) when compared with the uneventful group (185+/-49, 97+/-21 and 8.7+/-3 respectively), p values were <0.001, <0.001 and 0.005 respectively, while; differences in serum creatinine were not significant (1.39+/-1.42 vs. 1.0+/-0.32 in the eventful vs. uneventful group, P= 0.11). The eventful group had significantly lower ejection fraction when compared to the uneventful group (52+/-9 vs. 56+/-7, P =0.047).

Role of Hs-CRP in the Prediction of Future Cardiovascular Events

A-CRP measured at admission and different follow up periods:

CRP level obtained at the index admission (CRP 0) and those obtained at one, four and eight months (CRP1, CRP2 and CRP3 respectively) were compared between the eventful and the uneventful group. There was no statistically significant difference between the eventful vs. the uneventful group regarding level of CRP 0 (P= 0.9). However, CRP1, CRP2 and CRP3 showed a statistically significant increase in the eventful group when compared with the uneventful group (P <0001, 0.004 and 0.01 respectively).

B-Pre-event CRP:

Pre-event Hs-CRP "CRP sample that preceded the event" in the eventful group was studied vs. Hs-CRP samples taken at 1, 4 and 8 months of follow up that were not followed by event within the same group (n =35 patients). Levels of pre-event Hs-CRP samples showed statistically significant rise in the compared to the Hs-CRP levels that were not followed by events at different stages of follow up (Pre-event CRP vs. CRP1, CRP2 and CRP3 respectively, p= 0.0005,0.03 and 0.0002) (Table 2).

An optimum CRP value for predicting events was obtained using receiver operating characteristic (ROC) analysis based on comparing pre-event CRP to CRP1, CRP2 and CRP3 not followed by events. The optimum cutoff value determined was 6.5, 8.5 and 7mg/l based on comparison with CRP1, CRP2 and CRP3 respectively with a sensitivity of 87%, 78% and 81% respectively, and a specificity of was 63%, 56% and 76% respectively (Figure 1).

Table 2: Pre-event Hs-CRP in the eventful group vs. Hs-CRP at follow up not followed by events:

CRP "not followed by events"		Pre-event CRP	P value
CRP 1	9.76 +/- 9.94	22.0 +/- 19.3	0.0005
CRP 2	11.09 +/- 12.75	22.0 +/- 19.3	0.03
CRP 3	6.34 +/- 3.47	22.0 +/- 19.3	0.0002

Subgroup analysis in the eventful group, data expressed in mean +/- standard deviation.

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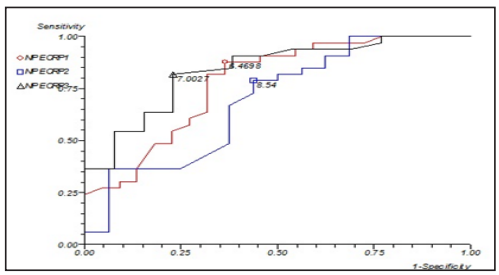

Figure 1: ROC plot for pre-event Hs-CRP in predicting events (Data derived from comparing pre-event CRP vs. NPECRP1 (red line), NPECRP2 (blue line) and NPECRP3 (red line) in the eventful group), NPECRP (non pre-event CRP).

We compared the percent change in Hs-CRP prior to the event vs. percent change that passed uneventful at different stages of follow up within the eventful group i.e. delta pre-event Hs-CRP vs. change from Hs-CRP1 to Hs-CRP2 not followed by events "non pre-event delta Hs-CRP2" and change from Hs-CRP2 to Hs-CRP3 "non pre-event Hs-CRP3". The magnitude of delta pre-event CRP showed statistically significant increase when compared with that not followed by events (P= 0.0003, P <0.0005 for delta CRP2 and CRP3 respectively). Based on the previous comparison, an optimum cutoff value of 4.3 folds rise in CRP was detected using ROC analysis with the highest sensitivity and specificity in predicting future cardiovascular events (sensitivity 78% and specificity 100%).

Angiographic Predictors of Serum Hs-CRP Level and Outcome in Patients with ACS

A- Coronary score:

In the studied cohort, patients who developed events had a statistically significant higher coronary score (11.7+/-5.9 vs. 9.0+/-6.1 in the eventful vs. the uneventful group, P= 0.045). However, Hs-CRP samples (CRP 0, CRP1, CRP2 and CRP3) showed no statistically significant correlation with the coronary score [(r= -0.019, 0.175, 0.155 and 0.064 respectively), (p= 0.85, 0.10, 0.17 and 0.56 respectively)].

B- Complexity of coronary stenoses:

The presence of complex coronary lesions was studied in the eventful vs. the uneventful group. The presence of more complex coronary anatomy predicted the occurrence of the study endpoints (p <0.001). There was a statistically significant positive relation between the complexity of coronary stenoses and Hs-CRP levels during different follow up visits (<0.001, 0.01 and <0.001 for CRP1, CRP2 and CRP3 respectively), but this relation was not significant with the admission Hs-CRP levels (p= 0.42) (Figure 2).

Multivariate Predictors of the Composite Endpoint of the Study

In a backward stepwise binary logistic regression analysis, pre-event Hs-CRP and cholesterol remained to be independent risk predictors after adjustment to other risk factors including age, diabetes and hypertension (Table 3).

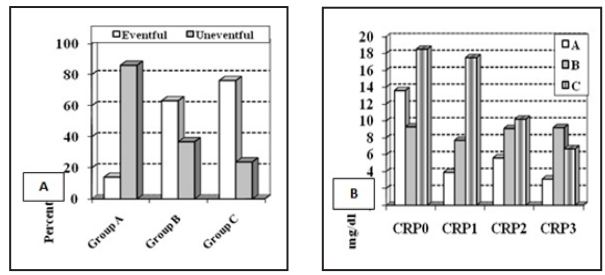

Figure 2: (A) Eventful Vs. uneventful cases among various categories of coronary stenoses, (B) Hs-CRP 0, 1, 2 and 3 compared among different categories of coronary stenoses.

Table 3: Multivariate predictors of the composite endpoint of cardiac death, non-fatal MI, and UA/NSTEMI in the 91 patient included in the study:

	Odds ratio	P value	Confidence interval	
			Upper bound	lower bound
Pre-event CRP	1.2	0.02	1.03	1.40
Age	1.04	0.33	0.95	1.13
Diabetes mellitus	0.18	0.02	0.04	0.74
Hypertension	0.15	0.02	0.03	0.77
Total cholesterol	1.02	0.008	1.005	1.034

DISCUSSION

Population Characteristics

In the present study; age, hypertension, diabetes and cholesterol (total and LDL cholesterol), impaired left ventricular ejection fraction and total leucocytic count were predictors of future cardiovascular events. This is in agreement with previous studies that studied age (7, 8), hypertension (9), cholesterol (9), diabetes (10, 11) impaired left ventricular ejection fraction (12) and total leucocytic count (13) as outcome predictors in acute coronary syndrome. The present study showed no predictive value for obesity and family history of CAD regarding cardiovascular events which is also in accordance with previous data. Gender that had controversial role in previous trials (7, 14) had no predictive power in our study. Serum creatinine, contrary to a previous studies (9, 15) was not predictive of future events.

Role of Hs-CRP in the Prediction of the Study Primary Endpoints

The present study showed no predictive value for Hs-CRP level done at admission. This finding could be attributed to the fact that the huge rise in CRP level is likely to reflect the inflammatory outburst that occur secondary to the occurrence of myocardial necrosis, leading to a disproportionate rise in this marker, rather than being explained by the inflammatory process taking place in the coronary arteries, leading to plaque rupture or formation of coronary thrombi (16). Several studies addressed this issue, some of which were concordant with our data (17, 18) while others could establish a role for admission Hs-CRP in predicting future cardiovascular events both at short term, in-hospital follow up or even at the long term follow up (19, 20).

Hs-CRP levels at follow up intervals were predictive of the occurrence of the study end points, being less likely confounded by the inflammatory contribution of myocardial necrosis. Few studies addressed the role of follow up Hs-CRP samples in the prediction of future cardiovascular events. Morrow et al. (21) studied the predictive role Hs-CRP at 30 days and 4 months in patients with non–ST-elevation or ST-elevation acute coronary syndrome for mortality. They found that patients with Hs-CRP >3mg/L at 30 days had significantly higher 2-year mortality rates compared to those with Hs-CRP ranging from 1 to 3mg/L or Hs-CRP <1mg/L (6.1% versus 3.7% versus 1.6%, P= 0.0001). Results were similar for Hs-CRP measured at 4 months. Data from a multicenter prospective study, the RIACS (22) (Recurrence and Inflammation in the Acute Coronary Syndromes) showed that follow up of Hs-CRP 1 month after acute coronary syndromes has a modest but not independent ability to predict composite end point of death, nonfatal MI and unstable angina [unadjusted odds (95% CI) was 1.23 (1.00-1.50), adjusted odds (95%CI) was 1.12 (0.93-1.34)].

We hypothesize that our data can reflect two groups of patients, according to the Hs-CRP levels, who have two distinctive patterns with different prognostic outcomes: a benign pattern, consisting of decreasing values from admission throughout follow up having a good prognosis and an adverse pattern, represented by those patients with persistently elevated values from admission throughout follow up having a worse outcome.

"Pre-event Hs-CRP", a term that was not addressed in previous trials, was compared with the Hs-CRP samples that was not followed by events at different follow up within the eventful group (n= 35). Also the percent change in Hs-CRP prior to the occurrence of event "Delta pre-event Hs-CRP" was examined vs. the percent change in Hs-CRP that was not followed by events, and in both situations pre-event Hs-CRP levels showed a statistically significant rise than the Hs-CRP levels that was not followed by events. According to our data, Hs-CRP level is a valuable marker for follow up of patients after ACS where rise in the absolute Hs-CRP level above an average of 7.3mg/l or 4.3 fold rise than the previous sample should raise the suspicion of a possible coronary event within the fore coming months and should dictate more aggressive form of medical therapy. Moreover, it supports the idea that Hs-CRP is not only a mere marker of instability of the atherosclerotic plaques, but is also a mediator for such instability through its pro-inflammatory and pro-atherogenic effects (23, 24).

Angiographic Data and Hs-CRP Levels

The absence of a correlation between high coronary scores and Hs-CRP levels at admission or at different stages of follow up shows that Hs-CRP identifies primarily the properties of the atherosclerotic plaque regarding inflammation and instability, whereas coronary score identifies the extent of atherosclerosis and perhaps these two measures of atherosclerotic disease are largely independent of each other's (25). These findings are in agreement with results reported by Azar et al. (26) and Arroyo et al. (27) meanwhile one study by Tataru et al. (28) could elucidate a strong correlation between CRP levels and the severity of CAD.

Complexity of coronary stenoses showed a statistically significant relation to the adverse outcome of the patients as well as to the CRP levels done at different follow up visits; these findings are in agreement with multiple previous studies (29, 30). However, no relation was found between Hs-CRP done at admission and the complexity of coronary stenoses, whereas previous studies elucidated such correlation (27). This may be attributed to different study designs, in our study we included all types of acute coronary syndrome including patients with STEMI, whom are expected to have the highest CRP surge 2ry to myocardial damage, which is considered a confounding factor.

LIMITATIONS

In the present study we did not use troponin to quantify the effect of the necrotic muscle mass on the rise of inflammatory markers, namely Hs-CRP. Hs-CRP in our study was measured up to 24 hrs after admission-which makes it likely to reflect underlying myocardial necrosis. During the follow up period not all patients were compliant to medical therapy especially statins which may have possibly altered the level of CRP among the study population at different follow up duration.

CONCLUSION

Hs-CRP done at admission in patients presenting with ACS could not detect the composite end point of unstable

angina, non-ST elevation myocardial infarction, ST elevation myocardial infarction and sudden cardiac death in the study population, meanwhile, Hs-CRP levels done at 1 month, 4 months and 8 months were predictive of the occurrence of the study endpoints. Pre-event Hs-CRP was significantly higher than all Hs-CRP samples not followed by events in a subgroup analysis involving the eventful group. A mean cutoff limit of 7.3mg/l showed the highest sensitivity and specificity in predicting the events.

Pre-event delta Hs-CRP was significantly higher in a positive direction when compared with delta Hs-CRP that was not followed by events in a subgroup analysis involving the eventful group. A cutoff of 4.3 folds increase was found to have the highest sensitivity and specificity. The previous data points out that Hs-CRP could be useful in following patients after acute coronary syndromes, whenever the absolute Hs-CRP level rises above 7.3mg/l or Hs-CRP level shows 4.3 or more fold increase, this should draw attention to a possible acute event within the fore coming months and may warrant intensification of medical therapy. The rise in the pre-event Hs-CRP also indicates that Hs-CRP may not be just a mere marker of plaque instability but also act as a mediator through its pro-inflammatory and pro-atherogenic effects. Pre-event Hs-CRP remains an independent risk predictor after correction to age, hypertension, Diabetes mellitus and the plasma cholesterol level.

Hs-CRP level at different follow up durations, but not on admission, was positively related to the complexity of coronary stenoses, but neither Hs-CRP at the index admission nor that at different follow up durations correlated with the coronary score as a surrogate to the total atherosclerotic burden, which reflects that Hs-CRP is not a mere marker of the angiographic atherosclerotic burden but instead, a marker of coronary artery disease activity.

Corresponding Author
Dr. Sameh Salama, MD, FSCAI
Cardiology Department, Cairo University, Cairo, Egypt.
E-mail: samehsalama70@yahoo.com

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