

**ANALYZING THE ROLE OF C-REACTIVE PROTEIN IN CARDIAC PATIENTS  
WITH UNSTABLE AND STABLE ANGINA**

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**Abstract**

**Background and objectives:**

Unstable angina is one of leading causes of hospital admissions for acute coronary disease, which accounts for >30% of admissions for acute myocardial infarction. This study was done to estimate the C-reactive protein level (CRP) as a marker of acute inflammation in patients with unstable and stable angina & to determine the prognostic value of CRP in coronary syndrome.

**Methods:**

A case control study was done including 40 cases of stable angina/control group (attending OPD) and 40 patients unstable angina/study group who are admitted to Intensive coronary care unit. Cases were selected according to inclusion and exclusion criteria in a prescribed Proforma. CRP estimation was done twice in study group and once in control group by latex agglutination method.

**Results:**

The study shows sex ratio 5:1 with maximum presentation between 4<sup>th</sup> to 6<sup>th</sup> decade with mean age of 53.1 years. In study group (unstable angina) CRP levels were elevated in 29 (72.5%) and 12(30%) in control (stable angina) group. Second sample was taken on 7<sup>th</sup> day of illness in study group; persistent elevated CRP levels were maintained in 7(17.5%) patients.

**Conclusion:**

Raised levels of CRP shows an evidence of growing inflammation at the coronary plaque and persistent elevated CRP levels in patients with unstable angina may indicate persistent instability of the disrupted plaque and is strongly related to the occurrence of subsequent ischemic complications. Serial evaluation of CRP plasmatic concentration may help in assessing the future ischemic events and thus help in preventing complications.

**Keywords:** CRP, Unstable angina, Stable angina, acute coronary syndrome.

**Introduction**

Atherosclerosis remains the leading cause of death and premature disability in developed societies. Reddy reported that from 1970 to 2015, mortality from Coronary artery diseases (CAD) was projected to almost double in the developing countries while it was projected to decline during the same period in the developed nations.<sup>1</sup> The Global Burden of Diseases (GBD) study reported the estimated mortality from CAD in India to be roughly 1.6 million in the year 2000.<sup>2</sup> Thus making it necessary to realize the causes, pathogenesis of these diseases and improve their diagnostic and treatment modalities as well as prophylactic programs. Inflammation is thought to be the key factor in the pathogenesis of atherosclerosis, from plaque initiation to subsequent growth and eventual rupture. The role of inflammation biomarkers testing in peripheral blood is increasing, with the C-reactive protein (CRP) being the most profoundly studied in cardiovascular diseases. CRP has become the most effective and sensitive marker for inflammation and unremarkable predictor of cardiovascular risk. It remains stable in samples over long periods of time and can be quite simply, rapidly and cheaply tested.<sup>3</sup> Elevated CRP has been shown to be associated with increased mortality in several settings, including acute coronary syndrome.<sup>5-6</sup> However, there still is controversy about the clinical use of CRP in this setting. A recent large prospective study did not support the incremental value of measuring CRP in acute coronary syndrome<sup>7</sup>. Conversely, multiple studies have also shown the association between increased CRP levels and increased cardiovascular disease (CVD) risk in patients with established disease, and the incidence of first cardiovascular events in individuals at risk for atherosclerosis.<sup>8</sup> Thus, present study attempts to investigate prognostic importance of CRP and also its role in inflammation in acute coronary artery syndrome pertaining to the category of unstable and stable angina patients.

### Material and methods

In this cohort study, we prospectively included patients admitted to medicine and cardiology at Chigatgeri general hospital and Bapuji hospital attached to JJM medical college, Davangere. The study included 40 cases of stable angina/control group (attending OPD) and 40 patients unstable angina/study group who are admitted to Intensive coronary care unit.

#### Inclusion criteria

Patients with angiographically proven coronary artery disease were included in this study.

#### Criteria for unstable angina cases

- New onset acute coronary syndrome < 1 month
- Worsening of previously stable acute coronary syndrome
- An episode of chest pain within previous 24 hours and no elevation of serum creatinine kinase & lactate dehydrogenase on admission.

#### Criteria for stable angina cases

Patients with angiographically proven coronary artery disease for more than 6 months duration and clinically stable myocardial infarction of more than 2 months duration & no clinically evident ischemic episodes during the previous week were included in this study.

#### Exclusion criteria

All patients with recent or ongoing infection or fever, chronic inflammatory disorders e.g. rheumatoid arthritis, systemic lupus erythematosus etc or any other condition which could have affected CRP levels were excluded from the study.

#### CRP estimation:

CRP levels were measured twice in study group, first sample was tested on the day of admission and 2<sup>nd</sup> sample was taken on the 7<sup>th</sup> day of illness respectively in study group, whereas in control group it was measured only once.

#### Principle

“Analyzing the role of C-reactive protein in cardiac patients with unstable and stable angina.”

This test is based on the immunologic reaction between CRP as an antigen and latex particles have been coated with monospecific anti-human CRP and sensitized to detect levels greater than 0.6mg/dl of CRP.

#### Procedure

##### Qualitative test

- One drop of serum placed in elevated area of slide with the help of disposable serum dropper.
- One drop of CRP latex antigen added to above drop and mixed well with disposable applicator stick
- Observed for agglutination by rocking the slide gently to and fro for 2 minutes.

##### Positive result

The presence of agglutination indicates content of CRP equal or greater than 0.6mg/dl

##### Negative result

The homogenous suspension of fluid (lack of agglutination) indicates CRP level less than 0.6mg/dl or within the normal range.

##### Semi- quantitative test

- A series of dilution of the test serum were prepared in normal saline e.g. 1:2,1:4,1:8 etc
- One drop of each of these dilutions is tested with one drop of latex CRP reagent.

- Agglutination was observed for no longer than 2 minutes on glass slide. The highest dilution which shows agglutination is taken as CRP titre of the test serum.

#### Results and interpretation

CRP levels were calculated in terms of micrograms per ml by multiplying the highest dilution giving clear cut agglutination with a factor of 6 (sensitivity of antigen 6µg/ml)

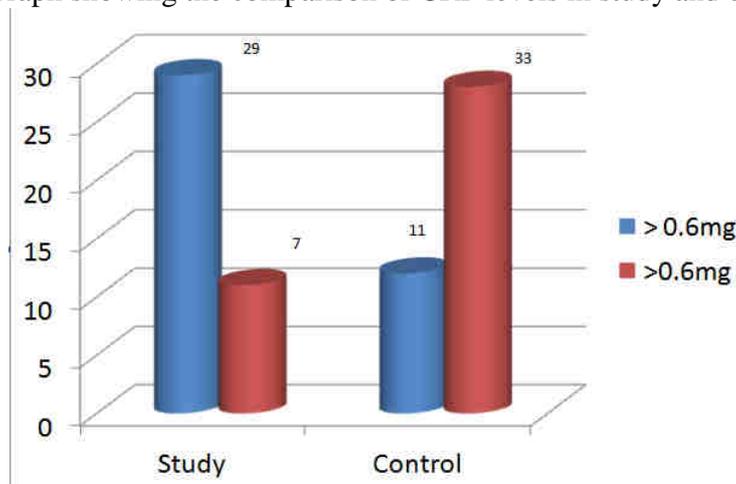
#### Results

The study showed maximum patients affected were between 4<sup>th</sup> to 6<sup>th</sup> decades with male predominance of sex ratio 5:1 with mean age 53.1 years. The 40 patients of the study group included new onset of angina (< 1 month) 27 (67%) patients, worsening of previously stable angina were 8 (20%) & 5 (12.5%) patients had previous myocardial infarction.

The CRP levels were elevated in 29 (72.5%) in study group in 1<sup>st</sup> sample and 12(30%) patients in control group, which shows highly significant value ( $p < 0.001$ ).

CRP levels came to normal in 22 out of 29 cases(82.5%) in 2<sup>nd</sup> sample in study group, whereas 7(17.5%) cases remained elevated , which was statistically highly significant ( $p < 0.001$ ).

**Graph 1:** Graph showing the comparison of CRP levels in study and control group.



**Table 1:** Comparison of CRP level in study and control group

“Analyzing the role of C-reactive protein in cardiac patients with unstable and stable angina.”

Test	Study		Control		Study V/s Control	
	>0.6mg/dl	<0.6mg/dl	>0.6mg/dl	<0.6mg/dl	X <sup>2</sup>	P
1 <sup>st</sup> sample	29(72.5%)	11(27.5%)	12(30%)	28(70%)	14.5	<0.001,HS
2 <sup>nd</sup> sample	7(17.5%)	33(82.5%)	-	-		

1<sup>st</sup> Vs 2<sup>nd</sup> test X<sup>2</sup>=24.4 p< 0.001, HS

**Table 2:** Mean CRP level in positive cases: CRP level ranges between 1.2-9.6mg/dl in study group with mean value of 3.5mg/dl. Whereas control group showed a range of 1.2-4.8 mg/dl with mean value of 2.5mg/dl.

	Study (N= 29)	Control	Study V/s Control	
			t <sup>*</sup>	P
Mean ± SD	3.5±2.5	2.5±1.5	1.31	0.20, NS
Range	1.2-9.6	1.2-4.8		

\*Unpaired t-test, p>0.005, not significant

**Table 3:** Table showing association with the prevalence of risk factors like hypertension, diabetes mellitus, obesity, smoking and elevated cholesterol level.

Risk factors	Hypertension	Diabetes mellitus	Obesity	Cholesterol elevation	Smoking	Alcohol
Study group	24(60%)	12(30%)	21(52.5%)	20(50%)	24(60%)	21(52.5%)
Control group	24(60%)	21(52.5%)	22(55%)	23(57.5%)	26(65%)	23(57.5%)
p value	NS	<0.05 S	NS	NS	NS	NS

## Discussion

CAD is emerging as a major health problem assuming epidemic proportions worldwide, particularly in the Indian subcontinent.<sup>9</sup> Prevention of CVD has become one of the most important public health challenges of our times. Several pliable and non-pliable factors are recognized as major risk factors for CVD and timely correction of these play vital role in prevention. Numerous studies have provided the evidence that inflammation plays a central role in the occurrence of CVD. Since vascular inflammatory changes can hardly be evaluated using cardiac imaging methods, the role of inflammation biomarkers testing in peripheral blood is increasing, with the CRP being the most profoundly studied in cardiovascular diseases.<sup>10-11</sup> Various epidemiological

studies have demonstrated that CRP is a strong predictor of future cardiovascular events.<sup>12-13</sup> In terms of clinical application, CRP seems to be a stronger predictor of Cardio Vascular events than LDL and cholesterol, and it adds prognostic information at all levels of calculated Framingham risk. One more advantage of CRP is that its levels have been shown to be stable with little or no diurnal variation,<sup>14</sup> making CRP the most commonly used and best standardized inflammatory marker of CVD and metabolic disorders.<sup>15</sup> Several prior studies have reported elevated CRP levels but very few studies have analyzed the CRP levels during in-hospital treatment, especially in Indian population. So, the present study measured the plasma concentration of CRP twice, first time at the time of admission of patients in ICCU which

was elevated in majority of patients with unstable angina (72.5%) in 1<sup>st</sup> sample and 2<sup>nd</sup> time on 7<sup>th</sup> day of illness respectively in study group. The previously raised CRP levels came to normal in 22 cases during the in-hospital treatment, whereas in rest 7 cases, elevated CRP levels were maintained. There was significant difference in the 1<sup>st</sup> and 2<sup>nd</sup> sample in study group. The inflammatory process may be responsible for increase in CRP levels during the episodes of chest pain. Persistent elevated CRP level in study group (17.5%) may indicate progression of inflammation and thus predicting the future alarming ischemic events which can be monitored as a prognostic indicator. Study done by Schwedler et al described a model of early atherogenesis in which raised CRP levels accelerated atherosclerosis and modified CRP partly prevented plaque formation.<sup>16</sup> CRP levels were significantly increased in study group compared to controls, indicating increased vasoreactivity of the coronary plaque in unstable angina cases compared to the stable angina cases. 30 % of control group also showed the mild elevated levels of CRP suggesting future cardiac events & hence monitoring done to prevent the worsening of prognosis.

Our study also showed prevalence of risk factors like hypertension, diabetes mellitus, obesity, smoking and elevated cholesterol level, which is similar to many other studies.<sup>17</sup> It has been shown that the CRP levels are not only elevated in patients with Metabolic syndrome but may also predict the development of Metabolic syndrome.<sup>20</sup>

### Conclusion

Elevation of CRP in unstable angina during the day of admission at onset of chest pain were observed, which may indicate the presence of growing inflammation at the coronary plaque or myocardial necrosis. In patients who have recovered and are clinically stabilized, elevated CRP levels on the 7<sup>th</sup> day of illness suggests persistent instability of the disrupted plaque and is

strongly related to the occurrence of subsequent ischemic complications. Vice versa, a low CRP level in-hospital treatment could be an indicator of quiescence of the injured plaque. This information will be helpful in the selection of patients who are potential candidates for more aggressive therapy. Mild elevation of CRP levels in stable angina group suggests future cardiac events which would have been missed if only conventional risk measurements were used. Assuming that plasma CRP reflects future risk of CVDs, intervention which reduces CRP may be effective in preventing the occurrence of cardiovascular events. Serial evaluation of CRP plasmatic concentration may help in risk stratification of patients with Acute Coronary Syndrome.

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