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Original Article

Prognostic Role of High Sensitivity C- Reactive Protein in Acute Myocardial Infarction

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Abstract

Background: *C reactive protein (CRP) is an acute phase protein, whose concentrations increase during inflammatory states.CRP, a marker of inflammation has been shown to predict incident MI, stroke, peripheral arterial disease and sudden cardiac death. It has also been shown to predict risk of both recurrent ischemia and death among those with acute coronary syndromes. It has been found that hsCRP consistently predicts new coronary events in patients with MI and unstable angina. In acute Myocardial infarction, hsCRP consistently predicts recurrent MI independent of Troponins.*

The aim of the study was to examine the baseline hsCRP values in acute myocardial infarction and to compare it with normal population, so as to study the prognostic value of hsCRP in predicting acute myocardial infarction. Also to find out the correlation between CRP levels and in hospital complications and ST segment resolution after thrombolysis with streptokinase.

Materials and methods: *This was a case control study conducted in 50 patients admitted with acute ST elevation myocardial infarction within three hours of onset of index chest pain in the intensive coronary care unit under the department of medicine in a tertiary care centre in South kerala. Samples were sent for hs CRP at admission. All patients underwent thorough clinical examination and investigations. They were closely followed up for in hospital complications .ST segment resolution after thrombolysis were also assessed. 50 normal healthy age and sex matched individuals were also selected and studied.*

Results: *The study was conducted among 50 cases and 50 control groups. The mean hs CRP of cases were 4.35mg/L while that of control were 1.61mg/L. About 54% of the cases had hs CRP above 3 mg/L while only 32% of the control had above 3mg/L. Of the 50 cases who developed myocardial infarction 38% had anterior wall and 16% inferior wall myocadial infarction. Both inferior wall and right ventricular wall myocardial infarction was seen in 18%, while inferior wall and posterior wall myocardial infarction was seen in 18%.Rest 10% of the cases developed a combination of inferior, posterior and lateral wall myocardial infarction. Reperfusion was absent in 42% of cases who had mean hs CRP value of 4.51mg/L. Eight percent of cases who had mean hs CRP 7.8 mg/L died..The percentage of cases who developed in*

hospital complications of myocardial infarction like post infarction angina, cardiac failure, arrhythmias, and death were 28%,26%,34%,and 8% respectively.

Conclusions: *The hsCRP an inflammatory marker was significantly higher in cases with acute myocardial infarction. Higher levels of admission hsCRP levels were associated with increased in hospital complications including death, cardiac failure, arrhythmias and post infarction angina. Among the complications correlation of higher hsCRP levels with cardiac failure was statistically significant. Mortality after myocardial infarction was correlated with higher hs CRP levels. Higher hs CRP levels were significantly associated with lower rates of reperfusion after thrombolysis with streptokinase.*

Keywords: *hsCRP, myocardial infarction, streptokinase, thrombolysis, acute phase protein.*

Introduction

As we have entered the new millennium with better living standards, and availability of health resources, increasing life expectancy and decline of infectious diseases, diseases like coronary artery disease (CAD) and malignancies are emerging as leading causes of morbidity and mortality.[1] This shift in disease pattern resembles that seen in developed countries. It has also been observed that Indians are affected early, have more severe and malignant course of coronary artery disease than elsewhere. A variety of studies over the last few years have demonstrated that elevated C reactive protein occurs after acute coronary syndromes.[2] It has also been proved that this is related to later complications.

C reactive protein (CRP) is an acute phase protein, whose concentrations increase during inflammatory states.CRP, a marker of inflammation has been shown to predict incident MI, stroke, peripheral arterial disease and sudden cardiac death.[3,4] It has also been shown to predict risk of both recurrent ischemia and death among those with acute coronary syndromes in emergency rooms.[5,6]

Former CRP assays had a sensitivity of only 5 mg/L. This is detected only during significant inflammation. Here comes the role of high sensitivity CRP (hsCRP) assays (hs- CRP) which can detect even lower levels of CRP (0.2-0.7 mg/L). Recent studies in apparently healthy people show that CRP concentration in serum rise long before traditional symptoms of heart disease are noticed.[7] By this newer method, it has been found that those with hsCRP values 1-3 mg/L are at moderate risk and those with >3 mg/L are at high risk for future coronary artery disease. This highlights the fact that those who were considered normal previously are actually at risk for coronary artery disease. Studies about prognostic value of hsCRP in heart disease have shown that people with no evidence of CAD, but with elevated hsCRP have 3 times increased risk of Myocardial infarction than those with hsCRP< 5 mg/L.[8,9]

There is very little published data on high sensitivity CRP assay and correlation with Myocardial infarction. Few studies that have been done concentrated only on the traditional CRP assays. Strongest association with prognosis in myocardial infarction has been with fibrinogen and hsCRP [10,11].It has been found that hsCRP consistently predicts new coronary events in patients with MI and unstable angina.[12] In acute Myocardial infarction, hsCRP consistently predicts recurrent MI independent of Troponins [13]

The aim of the study was to examine the baseline hsCRP values in acute myocardial infarction and to compare it with normal population, so as to study the prognostic value of hsCRP in predicting acute myocardial infarction. Also to find out the correlation between CRP levels and in hospital complications

Materials and Methods

Our study was a hospital based case control study done in 50 patients admitted with a diagnosis of acute ST elevation myocardial infarction with in 3 hrs of onset of index pain. 50 normal healthy age and sex matched controls were selected by group matching for each 10 years increment of age. The

study was conducted in intensive coronary care unit, under department of medicine in a tertiary care hospital in South Kerala over a period of one year.

Inclusion criteria for the study was patients with Classical history of chest pain, ECG changes, and cardiac enzyme elevation presenting within 3 hours. Only first episode of Myocardial infarction was taken and all of them were thrombolysed with streptokinase.

Exclusion Criteria for the study was (1) People presenting 3 hrs after the onset of prolonged chest pain. (2)Patients with pre-existing coronary artery disease, including those with past history of Myocardial infarction. (3)Non ST elevation MI and unstable angina. (4)Patients with fever at admission or within 3 weeks of admission. (5) Those with previous diagnosis of Rheumatoid arthritis, SLE, Chronic bronchitis or any other inflammatory disease, which could increase CRP levels. (6)LBBB with chest pain. (7)Those with contraindications for thrombolysis.

A detailed proforma was filled up for each patient, which included age, sex, presence of risk factors like hypertension, diabetes, smoking, BMI, family history of coronary artery disease in first degree relatives. Physical examination, laboratory parameters like ESR, CPK level after MI, hSCRP levels at admission, ST elevation in ECG at admission and 1 hour after thrombolysis and the in hospital complications. Echo cardiogram was done twice in all patients at admission and after 2 weeks. hSCRP was measured at admission to ICCU, within 3 hrs for all patients[19]. since CRP has no diurnal variation and no relation with food intake, a fasting sample is not required. A fasting sample was obtained to measure lipid profile. CPK MB was rechecked in all patients with chest pain after 24 hours of admission. ECG was repeated 1 hr after thrombolysis. The total ST elevation in millimeters was compared in the two ECGs and percentage of ST resolution after thrombolysis was noted. Those with >70% ST segment resolution were considered as fully reperfused. <30% were considered as not reperfused and between 30-70% were partially reperfused.

Results

The study was conducted among 50 cases and 50control groups. The age of the patients varied from 30 to 80 years. The number of patients were more in the age groups between 51 to 60 years and 51 to 60 years. (30% in each groups).(Table 10). The mean age of the cases and controls were comparable. There was no statistical difference in the mean age of cases and controls.(Table 2). The number of patients with diabetes, hypertension smoking, obesity, family history of coronary disease, dyslipidemia were 17(34%), 11(22%), 36(72%), 18(36%),30(60%) respectively.(Table 3).

The hs CRP values of both cases and control were studied. The mean hs CRP of cases were 4.35 while that of control were 1.61.Thus the mean hsCRP of cases was significantly higher than the controls.(Table 4). About 54% of the cases had hs CRP above 3 mg/L while only 32% of the control had above 3mg/L.(Table 5). Of the 50 cases who developed myocardial infarction 38% had anterior wall and 16% inferior wall myocadial infarction. Both inferior wall and right ventricular wall myocardial infarction was seen in 18%, while inferior wall and posterior wall myocardial infarction was seen in 18%. Rest 10% o the cases developed a combination of inferior, posterior and lateral wall myocardial infarction.(Figure 1)

Relation between hs CRP levels and reperfusion at 90 minutes after thromolysis with streptokinase were studied and was found to be statistically significant.(Table 60). As the mean hsCRP levels increased reperfusion after thrombolysis was lower. Reperfusion was absent in 42% of cases who had mean hs CRP value of 4.51mg/L. We also studied relation between hsCRP and death (Table 7). Eight percent of cases who had mean hs CRP 7.8mg/L died. So there was statistically significant elevation of hsCRP in those who died. The in hospital complications of myocardial infarction was studied.(Figure 2). The percentage

of cases who developed post infarction angina, cardiac failure, arrhythmias, and death was 28%, 26%, 34%,and 8% respectively. There was a significant increase in in hospital complications when the mean hsCRP levels increased. (Table8).

Table 1 Distribution according to age

Age	Cases				Controls		
	Total	Males	Females	Total %	Total	Male	Female
<30	0	0	0		0	0	0
30-40	1	1	0	2	1	1	
41-50	13	13	0	26	14	14	
51-60	15	13	2	30	14	12	2
61-70	15	15	0	30	16	16	
71-80	6	6	0	12	5	5	

Table 2 Comparison of mean age of cases Vs Controls

	Cases	Controls	Std. Deviation	P Value
Total	58.6	57.61	10.54	0.734
Males	58.04	57.08	10.77	0.72
Females	58.73	57.52	10.50	0.64

Table 3. Distribution of Risk Factors

Risk factor	Total cases		Controls		
	Number	%	Number	Percentage	P value
Hypertension	17	34%	15	30%	0.83
Diabetes	11	22%	12	24%	1
Smoking	36	72%	30	60%	0.86
Obesity	18	36%	15	305	0.2
Family history	18	36%	10	20%	0.118
Dyslipidemia	30	60%			

Table 4 Comparison of hsCRP of Cases Vs Controls.

	Mean hs CRP	Std Devatation
Cases – 50	4.35	2.89
Controls – 50	1.61	1.82
Total – 100	2.98	2.82

Table 5. Distribution according to hsCRP values

	hsCRP<3mg/L	hsCRP>3mg/L
Cases	23(46%)	27(54%)
Controls	34(68%)	16(32%)

Table 6. hsCRP levels and reperfusion after thrombolysis

		Mean hsCRP	Std Deviation
Fully reperfused	9 (18%)	2.58	2.04
Partially reperfused	20 (40%)	3.75	2.61
Not reperfused	21 (42%)	4.51	3.15

P value – 0.049

Table 7 Relation between hsCRP levels at admission and death.

		Mean hsCRP	Std Deviation
died	4(8%)	7.8	1.48
Survived	46 (92%)	4.06	232.909
Total	50	4.35	2.99313

P value – 0.05

Table 8 Distribution of In hospital complications

Complications	Number	%	hsCRP			P value
			Mean	< 3mg/L	> 3	
Angina	14	28%	4.45	6	8	0.81
Cardiac Failure	13	26%	5.18	3	10	0.05
Arrhythmias	17	34%	3.79	9	8	0.581
Not reperfused	21	42%	5.51	7	14	0.049
Death	4	8%	7.8	0	4	0.015
Re infarct	0	0	0	0	0	0

Figure 1 – Distribution of type of MI

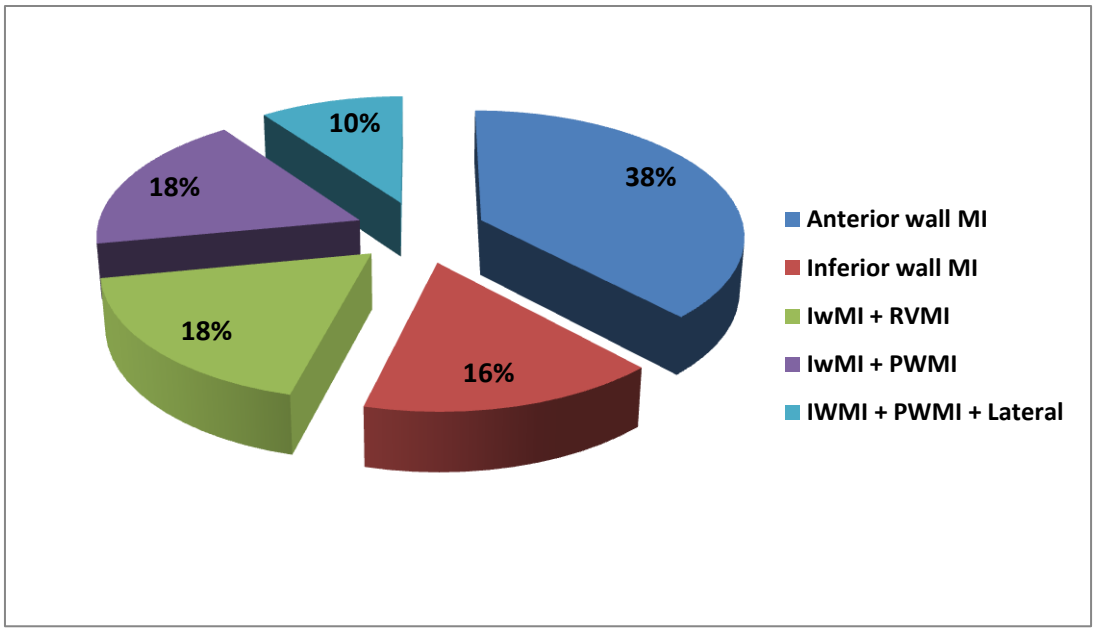
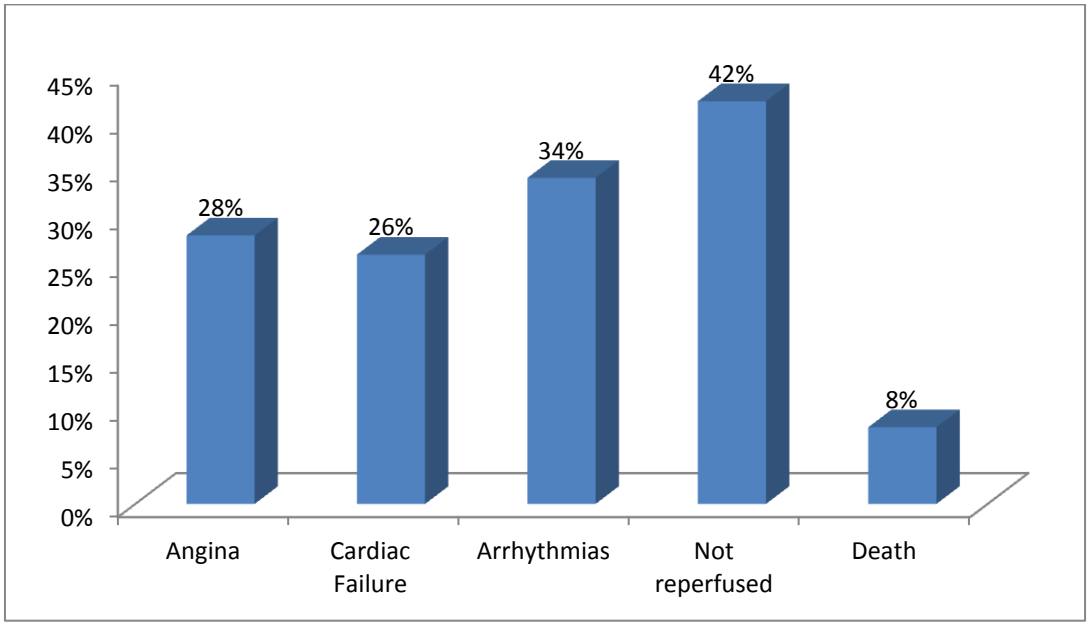


Figure 2 Distribution of in hospital complications



Discussion

The patients who were studied belonged to ages ranging from 36 yrs to 80 yrs with a mean age of 58.6. The sex ratio of patients was 24:1. 50 controls were selected who were age and sex matched. The mean age of controls was 57.6, which was similar to the cases. The pattern of Coronary artery disease (CAD) in India is such

that 51 to 60 years is the most common age group, which is a decade earlier than in developed countries.[14] Earlier age of onset in our population could be due to lifestyle factors, smoking, dietary habits or genetic factors. In all these previous trials, 80-90% cases of CAD were males.

The conventional risk factors of the patient population was analyzed. The most common risk factor was dyslipidemia. 100% of cases had LDL above l00mg/dL; of these 58% had LDL greater than 130mg/dL. The second most important risk factor was smoking, 72% of cases were smokers. Among controls 60% were smokers. Hypertension and diabetes were risk factors in 34% and 22% of cases respectively. Among controls it was 30% and 24%. 72% of cases were above the age of 50 yrs. A family history of coronary artery disease among first degree relatives was present in 36% of cases and 20% of controls. The mean Body mass index was 24.59 for cases and 23.86 for controls. The risk factors were almost equal among cases and controls and had no statistically significant difference.

The most common symptom of patients was chest discomfort (96% of patients). Only eight percent had breathlessness at admission. The most common type of MI was Inferior wall MI (62%) either alone or in combination with RVMI/or Posterior wall MI. 38% had Anterior wall MI. The in hospital complications were studied using clinical parameters and echocardiogram. All patients were monitored till discharge, atleast for 2 weeks. It was observed that arrythmias occurred in 34% of cases, cardiac failure occurred in 26%. Post infarction angina occurred in 28% and 42% cases had less than 30% ST resolution even after thrombolytic treatment and eight percent of cases expired. In western trials AWMI is most common (60%) as in Toshihisa et al.[15] Exact reason for this is not clear.

The mean levels of hscRP was 4.35 ± 2.99 in cases compared to 1.61± 1.82 in controls. There was statistical significance in this result analysed by ANOVA table. P value was <0.001. Thus patients with acute Ml had a higher hsCRP level at admission, than those without CAD. 68% of controls had hsCRP< 3 of which 60% were in normal range. (0.2- 0.7 mg/L)

The mean hsCRP at admission in the Gupta et al study was 6.3 mg/1, which is above the normal range as in our study.[16] The mean peak CRP was 14.1 in Toshihisa et al study. It is higher because the peak value was measured three days after acute MI. The IHC trial showed a mean CRP was 2.5 mg/dl. All these studies show that CAD occurs in persons with elevated hsCRP.

Patients in our study were categorized into those with hsCRP<3mg/l and >3mg/l. In our study, 46% had hsCRP less than 3mg/L If hscRP is taken as a criteria for severity, our patients are having a milder form of CAD. More over a vast number of our patients (46%) had hSCRP <3mg/L. These patients cannot be diagnosed by routine CRP assays. This highlights the importance of hSCRP as a predictor of future Coronary disease.

All the in hospital complications were co-related with mean hscRP levels at admission, Also patients were categorized into those with hscRP<3 mg/L and with >3mg/L. The inhospital complications were compared between these subgroups. Of the 34% of cases who developed arrythmias in hospital mean hsCRP was 3.79, which was less than those without arrythmias. This was of no statistical significance. None of the studies correlated hsCRP with occurrence of arrythmias.

Mean hscRP of patients with post infarction angina (28%) in our study was 4.45, where as it is only 3.82 in those without angina. This had no statistical significance. But 58% of those with post infarction angina had hscRP>3 mg/L . No other studies correlate hsCRP and post infarction angina.

Mean hsCRP of patients with cardiac failure in our study was 5.18, where as it was only 4.06 in others. 26% had cardiac failure in hospital. Of those with cardiac failure, majority (77%) had hscRP>3mg/L. This was of statistical significance. P Value <0.05 by fischers exact test. Among 38% of controls with elevated hsCRP, 55% had

hypertension and 50% had diabetes, 70% of them were smokers. This might account for the higher hsCRP values in these control subjects. It is a possibility that controls with elevated hsCRP may develop CAD in future as hsCRP levels rise even before established CAD. In our study eight percent of patients died. The mean hsCRP in them was 7,8, where as survivors had a mean hsCRP of 4.06. All the patients who died had a mean hsCRP>3. This had statistical significance. P Value <0.05. This is similar to Toshihisa et al and Gupta et al results. 10% died in Toshihisa et al and 14% died in Gupta et al study. Mean hsCRP of mortality group was 8 times higher than survivor group in Gupta et al study. As in our study, CRP is 2.5 times higher in mortality group than survivors in Toshihisa et al. In all the studies high hsCRP is related with death after acute MI and had statistical significance. None of our patients had reinfarction.

42% of patients had less than 30% resolution of ST segment after thrombolysis. Mean hsCRP was 4.51 in this group, compared with 2.58 in those with greater than 70% ST resolution. Those with 30 - 70% reperfusion (partially reperfused) had mean hscRP of 3.75. There was statistically significant increase of hsCRP in patients who were not reperfused, based on ST resolution (P value<0.05) None of the previous studies correlated CRP with percentage of ST segment resolution after acute MI. Thus hsCRP can be used as a prognostic factor for assessing reperfusion and to know about the progress of the disease.

Thus from analysis it is understood that cases with acute MI had elevated hsCRP compared to controls. Those with in hospital complications like cardiac failure, death and reduced ST resolution had elevated CRP. Mean hsCRP of cases was 4.359.

The study was conducted in a small population in a tertiary care centre. In future we need large scale studies which may give more information regarding the prognostic significance of hsCRP after acute myocardial infarction. Long term follow up studies on healthy individuals can also be done as a large population based prospective study. But years of follow up may be needed. Those with hs-CRP elevation should be advised life style modification

Conclusions

The hsCRP a cardiac inflammatory marker was significantly higher in cases with acute myocardial infarction. Higher levels of admission hsCRP levels were associated with increased inhospital complications including death, cardiac failure, arrhythmias and post infarction angina. Among the complications correlation of higher hsCRP levels with cardiac failure was statistically significant. Mortality after myocardial infarction was statistically correlated with higher hsCRP levels. Higher hsCRP levels were significantly associated with lower rates of reperfusion after thrombolysis with streptokinase.

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