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Peri-operative High Sensitive C-reactive Protein for Prediction of Cardiovascular Events after Coronary Artery Bypass Grafting Surgery in Left Ventricular Dysfunction Patients: A Prospective Observational Study

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Abstract

High sensitivity C-reactive protein is inflammatory marker having predictive value in both stable and unstable angina as well as in the acute phase after coronary artery bypass grafting. Many studies have evaluated the prognostic value of CRP for predicting post-operative outcome, most have focused on pre-operative CRP levels, which cannot reflect the inflammatory reactions induced by surgery itself. Here author hypothesized that post-operative CRP elevation, reflecting surgery-induced inflammatory reactions, is related to the occurrence of post-operative major adverse cardiovascular and cerebral events (MACCE) in patients undergoing off-pump coronary artery bypass surgery (OPCAB). *Objective:* To better understand the current state and application of high sensitivity C-reactive protein (hs-CRP) in clinical practice. To establish excellence of hs-CRP level as a prognostic marker in low EF heart patients. We have done prospective observational study in peri-operative period of 100 patients with stable ischemic heart disease and left ventricular dysfunction (EF < 35%) who underwent off pump CABG to ascertain whether an activation of the inflammatory system during surgery, detected by elevated serum hs-CRP, has any association with prognosis. *Result:* In patients with pre-operative hs-CRP ≥ 1.0 mg/dl, the cumulative event incidence was 38% compared to 15% in patients with levels pre-operatively of hs-CRP less than 1.0 mg/dl. Post-operative hs-CRP has no significant difference. *Conclusion:* Author conclude that increased pre-operative hs-CRP > 1.0 mg/dl predict in hospital cardiac and cerebrovascular morbidity and mortality. There is increase in post-operative hs-CRP but it is not statistically significant to conclude it as prognostic marker for predicting post-operative morbidity.

Keyword: C-reactive Protein; CABG; Prognosis; Inflammation.

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Introduction

Coronary Artery Bypass Graft (CABG) is the most common cardiac surgery which has both early and late post-operative complications.[1] Early complications include stroke, myocardial infarction, hemodynamic instability and long ICU stay.[2] Atherosclerosis, underlying cause of most Coronary Heart Disease, is basically Systemic as well local inflammation in arterial wall and

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shoulder region of plaque is heavily infiltrated with inflammatory cells.[3,4] As it is inflammation, inflammatory markers must be elevated across the clinical spectrum of atherosclerotic coronary artery disease.[5,6]

High sensitive C-reative Protein (hs-CRP) is used to detect the low level inflammation when CRP is within the normal range. Elevation of hs-CRP is associated with a poor prognosis in patients with acute myocardial infarction (AMI).[7] The recognition that active inflammatory processes may destabilize the fibrous cap tissue, thus triggering plaque rupture and enhancing the risk of coronary thrombosis.[8,9] Many studies have evaluated the prognostic value of CRP for predicting post-operative outcome, most have focused on pre-operative CRP levels, which cannot reflect the inflammatory reactions induced by surgery itself.[10,11]

In current study, author hypothesized that peri-operative hs-CRP elevation is related to the occurrence of post-operative major adverse cardiovascular and cerebral events (MACCE) in patients undergoing Off-pump Coronary Artery Bypass (OPCAB) surgery with left ventricular dysfunction. Author investigated the predictive value of a peri-operative high sensitivity CRP on 30 days mortality after elective OPCAB surgery.

They studied 100 patients with stable ischemic heart disease and left ventricular dysfunction (EF < 35%) who underwent off pump CABG to ascertain whether an activation of the inflammatory system during surgery, detected by elevated serum hs-CRP has any association with prognosis.

Materials and Methods

This study was done at tertiary care hospital. Study population of 100 patients were enrolled in following approval by the local ethical committee approval and getting informed, written consent of patients. This is prospective observational study.

Inclusion Ccriteria

Patients scheduled for off-pump Coronary Artery Bypass Grafting (CABG) surgery, less than *75 years* and with left ventricle ejection fraction less than 35%.

Exclusion Criteria

Chronic obstructive pulmonary disease, recent myocardial infarction, acute or chronic renal disease (serum creatinine > *2 mg/dl*), chronic liver disease (total bilirubin > *3 mg/dl*), treatment with intravenous nitrates or inotropes before surgery, redo cardiac surgery, treatment with steroids in the previous six months, previous percutaneous coronary intervention, cerebrovascular accident during the year prior to the study, current inflammatory condition or history of a neoplastic condition.

The number, type and severity of diseased coronary arteries were determined based on angiography of the patient. Artery was considered to be diseased if the stenosis was equal or greater than 60% of the luminal diameter.

Anesthesia and Surgery

A single surgical and anesthesia team involved incurrent study. All patients underwent general anesthesia according to standardized protocol. After endotracheal intubation, 50% O_2, 50% air, and 1% to 2% sevofluranewas used for all patients. Antifibrinolytic agents were not used. Intra-operative TEE was done to document regional wall motion abnormality. Patients were transferred to the surgical Intensive Care Unit (ICU) after CABG and extubated there only after achieving extubation criteria. Patients older than *60 years* with a hemoglobin value less than *9 g/dl* and patients aged *60 years* or less with a hemoglobin value less than *8 g/dl* received packed red blood cells. Patients with a tendency to bleed were treated by transfusion of fresh frozen plasma and platelet concentrate. Inotropes were used only when hemodynamic stabilization could not be achieved by fluid administration or when there was other evidence of impaired contractility. In case of an insufficient response to inotropes, intra-aortic balloon counter pulsation was initiated at the discretion of intensivist.

Data collection

Fasting blood samples were collected from a peripheral vein before the operation. Post-operative blood samples were taken from indwelling CVP line. Peri-operative White Blood Cells (WBC), Platelets (PLT), Hemoglobin (Hb), S. creatinine, S. total bilirubin, SGOT and SGPT levels were measured by certified technician in the central biochemical and clinical laboratory. Pre-operative hs-CRP was taken within *3 days* prior to surgery and Post-operative Troponin I and hs-CRP level was measured at *12 and 24 hours* post-operative from central vein sample. A highly sensitive CRP (hs-CRP) analysis was performed using the commercially available kit of abbott CRP vivo an

automated blood test that uses particle-enhanced immunoturbidimetric method to quantify CRP in serum samples.

Definition of post-operative MACCE (Major adverse cardiovascular and cerebral events).

The primary endpoint was post-operative MACCE, which was defined as a composite of death from cardiac causes and stroke. Cardiac cause include MI, cardiac arrhythmia, or heart failure caused primarily by a cardiac problem. Stroke was defined as a new ischaemic or hemorrhagic cerebrovascular accident with a neurological deficit lasting more than *24h*. The diagnosis of MI was based on the associated with cardiac biomarker levels more than five times the upper reference limit.

Recent myocardial infarction (MI) was defined as myocardial infarction less than *30 days* at the time of surgery.[12] Patients were followed up to *30 days* after surgery and events recorded include:

(1) Death from cardiovascular causes.[13]

(2) Ischemic stroke[13] (defined as new ischemic or hemorrhagic cerebrovascular accident with a neurological deficit lasting more than *24h* with definite image evidence by head computer tomography).

(3) Hemodynamic instability due to Low Output Systemic heart failure[14] (LOF) (defined as needing one of the following: Intra-operative Intra-aortic Balloon Pump (IABP), return to graft revision, or ≥ two inotropes at *48 hours* post-operatively).

(4) Myocardial infarction or damage[15,16] (defined as elevated troponin I (Tn I) greater than *10.0 µg/l* at *12 hours* after surgery associated with characteristic Electrocardiographic (ECG) changes (development of new Q waves or new persistent ST-T change) or echocardiographically documented new dyskinetic-akinetic segment).

Use of inotropic agents and Intra-aortic Balloon Pump (IABP), Mechanical ventilation (MV) duration, lengths of Intensive Care Unit (ICU), hospital stay, number of grafts and peri-operative red blood cell transfusion were recorded. All data were collected prospectively.

Deaths were classified as either cardiac or non-cardiac. Deaths that could not be classified were considered cardiac. Hospital mortality is defined as all deaths within *30 days* of surgery, irrespective of where the death occurred, and all deaths in the hospital after *30 days* among patients who had not been discharged after undergoing surgery.

Results

Categorical variables are presented as numbers and percentages and analysed using the χ_2-test. Continuous variables are assessed for normal distribution and presented as means and standard deviation. Continuous variables are compared using student's *t*-test for normally distributed variables and the mann-whitney U test for non-normally distributed variables. The level of significance was accepted at $p < 0.05$. Statistical analysis was performed using SPSS, version 20.0 (Chicago, IL, USA).

In current study, both the groups were comparable with regards to age, sex, weight, height, body surface area, left ventricular ejection fraction, comorbidities, coronary artery involvement and medical management ($p > 0.05$), below shows (**Table 1**). During the first *30 days* after surgery, 78 patients were free from observed events and 22 patients developed following cardiovascular events: 8 (36.36%) had myocardial damage or infarction, 8 (36.36%) had low output heart failure, 4 (18.18 %) suffered cerebrovascular accident and 2(9.09%) patients were dead.

Table 1: Demographic and medication data according to Major Adverse Cardiovscular and Cerebral Events (MACCE).

Data	Without events (n = 78)	With events (n = 22)	*p* - value
Demographics			
Age, years	57.54 ± 8	54.64 ± 7.47	0.131
Gender,			
M	65	19	0.98
F	13	3	
BSA, m^2	1.67 ± 0.17	1.67 ± 0.15	0.954
Comorbidities			
DM	15	4	0.8439
HTN	6	1	0.9698
DM + HTN	6	1	0.9698
Angiography			
SVD	5	2	0.9698
DVD	30	9	0.9684
TVD	43	11	0.854
Echocardiography			
LVEF %	30.26 ± 5.22	29.78 ± 5.46	0.704
Medications			
Beta blockers	59	19	0.4349
ACE inhibitors	30	8	0.9445
Nitrates	19	6	1
Statins	55	13	0.4499
Diuretics	28	7	0.9194
Aspirin	50	12	0.5707

The impact of pre- and intra-operative clinical variables, according to chi-square test, on combined post-operative cardio-vascular event is shown in belo shows (**Table 2 & 3**). There is significant correlation of pre-operative hs-CRP with blood transfusion, ventilation duration, ICU stay and

Table 2: Clinical data according to Major Adverse Cardiovscular and Cerebral Events (MACCE).

Data	Without events (*n* = 78)	With events (*n* = 22)	*p* – value
Hematology			
WBC/*cmm*	9676.54 ± 2654.74	9308.19 ± 2351.67	0.558
Post-op WBC/*cmm*	14674.62 ± 4963.73	14683.64 ± 5296.97	0.994
Hemoglobin, *gm/dl*	12.66 ± 1.63	12.86 ± 2	0.636
Post-op Hemoglobin, *gm/dl*	10.9 ± 1.29	10.54 ± 1.41	0.258
Platelet/*cmm*	293826.93 ± 98296.93	269609.1 ± 64739.7	0.279
Post-op Platelet/*cmm*	159903.85 ± 85962.32	150318.19 ± 50930.82	0.62
Pre-creatinine, *mg/dl*	0.99 ± 0.29	1.02 ± 0.26	0.615
Creatinine, *mg/dl*	1.093 ± 0.307	1.164 ± 0.44	0.392
Pre-Billirubin, *mg/dl*	0.85 ± 0.44	0.77 ± 0.56	0.482
Post-op Billirubin, *mg/dl*	1.43 ± 0.97	1.25 ± 1.11	0.473
Pre-hs-CRP, *mg/dl*	0.7 ± 0.69	1.6 ± 2.35	0.03
Post-op hs-CRP *12 hr, mg/dl*	5.81 ± 4.32	4.58 ± 3.83	0.231
Post-op hs-CRP *24 hr, mg/dl*	12.07 ± 7.39	12.76 ± 6.68	0.693
Troponin I, µg/l	1.45 ± 2.15	7.47 ± 7.52	0.0001
RBS, *mg/dl*	175.22 ± 157.06	136.37 ± 29.82	0.253
RBS *12 hr, mg/dl*	165.15 ± 38.65	161.69 ± 36.75	0.709
RBS *24 hr, mg/dl*	163.42 ± 28.71	171.87 ± 44.35	0.287
Pre-Lactate, *mmol/l*	1.41 ± 0.52	1.44 ± 0.86	0.849
Post-op Lactate *12 hr*, *mmol/l*	3.03 ± 1.74	4.2 ± 2.64	0.15
Post-op Lactate *24 hr, mmol/l*	2.22 ± 0.78	2.63 ± 0.89	0.32
Pre-Ph	7.39 ± 0.04	7.39 ± 0.04	0.888
Post-op Ph *12 hr*	7.37 ± 0.05	7.39 ± 0.06	0.293
Post-op Ph *24 hr*	7.38 ± 0.04	7.36 ± 0.05	0.067
SVO2 %	70.15 ± 8.44	69.23 ± 7.27	0.643
Post-op SVO_2 *12 hr*, %	67.97 ± 7.44	69.21 ± 6.46	0.478
Post-op SVO_2 *24 hr*, %	67.62 ± 6.66	66.6 ± 7.18	0.538
Surgery			
Number of grafts	2.72 ± 0.83	2.5 ± 0.68	0.256
RBC transfusion, unit	1.26 ± 1.47	2.37 ± 1.82	0.004
Ventilation time, hours	5.99 ± 4.22	16.96 ± 18.85	< 0.0001
ICU Stay, days	3.33 ± 1.04	6.46 ± 7.38	< 0.0001
Hospital stay, days	6.81 ± 2.56	9.55 ± 6.62	0.004

Table 3: Demographic and medication variable according to pre-op hs-CRP > *1.0 mg/dl* or ≤ *1.0 mg/dl.*

Data	Pre-op hs-CRP < *1 mg/dl* (*n = 71*)	Pre-op hs-CRP ≥ *1 mg/dl* (*n = 29*)	*p* - value
Demographics			
Age, years	57.17 ± 7.1	56.25 ± 9.83	0.599
Gender,			
F	14	2	0.1983
M	57	27	
BSA, m^2	1.67 ± 0.16	1.67 ± 0.17	0.835
Comorbidities			
DM	15	4	0.5705
HTN	5	2	0.6713
DM + HTN	4	3	0.6848

Data	Pre-op hs-CRP < *1 mg/dl* (*n = 71*)	Pre-op hs-CRP ≥ *1 mg/dl* (*n = 29*)	*p* - value
Angiography			
SVD	4	3	0.6848
DVD	29	10	0.7144
TVD	38	16	0.9436
Echocardiography			
LVEF %	29.93 ± 5.11	30.69 ± 5.63	0.514
Medications			
Beta blockers	55	23	0.9491
ACE inhibitors	26	12	0.8275
Nitrates	19	6	0.7027
Statins	48	20	0.9172
Diuretics	28	7	0.2208
Aspirin	47	15	0.2602

Table 4: Clinical data according to Pre-op hs-CRP < *1.0 mg/dl OR* ≥ *1.0 mg/dl*

Data	Pre-op hs-CRP < *1 mg/l* (*n = 71*)	Pre-op hs-CRP ≥ *1 mg/l* (*n = 29*)	*p*- value
Hematology			
WBC/*cmm*	9626.62 ± 2442.87	9519.32 ± 2946.92	0.852
Post-op WBC/*cmm*	14914.09 ± 5039.57	14095.18 ± 4981.3	0.461
Hemoglobin, *mg/dl*	12.75 ± 1.75	12.58 ± 1.63	0.655
Post-op Hemoglobin, *mg/dl*	10.83 ± 1.37	10.78 ± 1.19	0.841
Platelet/*cmm*	296161.98 ± 98910.89	269737.94 ± 71430.33	0.195
Post-op Platelet/*cmm*	157759.16 ± 85470.43	157882.76 ± 63717.8	0.994
Pre-Creatinine, *mg/dl*	1 ± 0.3	0.98 ± 0.24	0.833
Creatinine, *mg/dl*	1.122 ± 0.36	1.074 ± 0.271	0.524
Pre-Billirubin, *mg/dl*	0.84 ± 0.49	0.8 ± 0.4	0.695
Post-op Billirubin, *mg/dl*	1.44 ± 1.03	1.27 ± 0.93	0.457
Post-op hs-CRP *12 hr, mg/dl*	5.34 ± 4.02	6.02 ± 4.76	0.47
Post-op hs-CRP *24 hr, mg/dl*	11.93 ± 7.27	12.95 ± 7.13	0.525
Troponin I, µg/l	2.45 ± 4.56	3.58 ± 4.93	0.275
RBS, *mg/dl*	174.17 ± 164.79	148.32 ± 32.37	0.405
RBS 12 hr, mg/dl	164.67 ± 38.49	163.69 ± 37.73	0.908
RBS *24 hr, mg/dl*	67.43 ± 6.78	67.29 ± 6.83	0.926
Pre-Lactate, *mmol/l*	1.4 ± 0.56	1.46 ± 0.72	0.635
Post-op Lactate *12 hr, mmol/l*	3.03 ± 1.7	3.93 ± 2.55	0.041
Post-op Lactate *24 hr, mmol/l*	2.34 ± 0.87	2.22 ± 0.89	0.536
Pre-Ph	7.39 ± 0.04	7.38 ± 0.04	0.093
Post-op Ph *12 hr*	7.37 ± 0.05	7.38 ± 0.05	0.369
Post-op Ph *24 hr*	7.38 ± 0.04	7.37 ± 0.05	0.302
Surgery			
Number of grafts	2.68 ± 0.76	2.66 ± 0.9	0.905
RBC transfusion, Units	1.31 ± 1.51	1.97 ± 1.77	0.063
Ventilation time, *hrs*	7.17 ± 9.09	11.42 ± 13.02	0.066
ICU Stay, days	3.69 ± 2.4	4.83 ± 5.87	0.167
Hospital Stay, days	7.41 ± 3.22	7.42 ± 5.45	0.995
MACCE	11	11	0.0284

hospital stay. Twenty nine patients had elevated serum concentration pre-operatively of hs-CRP ≥ *1.0 mg/dl* ($p = 0.028$). (**Table 4)** shows the distribution of other pre-operative variables according to high sensitivity CRP less than 1.0 mg/dl or ≥ 1.0 mg/dl. With preoperative hs-CRP ≥ 1.0 mg/dl, the cumulative event incidence was 38% compared to 15% in patients with levels pre-operatively of hs-CRP less than *1.0 mg/dl*. Serum concentration of pre-operative hs-CRP ≥ *1.0 mg/dl* was independent predictors of combined cardiovascular event after CABG surgery. Post-operative lactate at *12 hour* and ventilation time is significantly affected by pre-operative hs-CRP ≥ *1.0 mg/dl*.

Discussion

As far as author knows no study has been done for prediction of cardiovascular events in patients with dysfunctional heart undergoing CABG surgery based on pre and post-operative hs-CRP. In current study, author concluded that pre-operative serum concentrations of hs-CRP > *1.0 mg/dl* is associated with a significantly increased risk of overall post-operative cardiac death, myocardial infarction, low cardiac output syndrome and cerebrovascular accidents. Immediate post-operative hs-CRP does not appear to be a useful biomarker in the outcome after cardiac surgery as pre-operative hs-CRP.

CRP has been shown to be a strong predictor of early and long-term outcome after percutaneous coronary intervention and peripheral vascular surgery.[17,18] A pre-operative CRP > *0.3 mg/dl* is associated with a significantly increased risk of late all-cause mortality, cardiac death. As vulnerable plaque is probably responsible for approximately half of peri-operative MI.[19,20]

There are very few authors who used hs-CRP which is used in our study. Serum concentration of hs-CRP ≥ *3.3 mg/l* was an independent risk factor of post-operative combined cardiovascular event in patients undergoing CABG surgery.[21] But average ejection fraction was 50% in this study. Cardiovascular events happen more often in dysfunctional heart. So, author studied predictive value of hs-CRP in dysfunctional heart patient undergoing CABG in Indian continent. And author find out that cut off limit of hs-CRP as independent risk factor for cardiovascular event is on lower side in low EF patients.This might be used to refine the predictive value of scores such as the Euroscore.[12] Further studies with larger number of patients are needed to allow generalization of our findings.

There is study showing no correlation of post of hs-CRP and post-operative outcome,[22] in valvular and coronary surgery. But here author have studied only in coronary surgery as this patients are more vulnerable for atherosclerosis plaque. In current study, post-operative hs-CRP at *24 hr* is higher in patient having cardiovascular event but statistically not significant. So if we follow it Post-erative day 2 & 3, we might get statistically significant result. But that is limitation of our study.

Factors that can affect peri-operative hs-CRP like pre-operative statin and other drug treatment, peri-operative total count, left ventricular ejection fraction and other demographic and clinical data are similar in both group of patients. There is always a limitation when relatively rare complications are analysed. Hs-CRP may be adversely affected by local or systemic infection which limits its utility for prognostic marker.[23] It is recommended that patients with a CRP of > *1 mg/d1* in the presence of active infection, should have the test repeated in *2 weeks*, as the clinical significance of the test is questionable.[23] Infections would be expected to increase false negative test results and decrease the utility of the test. In our study, pre and post-operative total WBC count and platelet count is comparable so there is less chance of infection associated inflammatory response. Though pre-operative hs-CRP is related with MACCE, it has no correlation with post-operative renal dysfunction or acute kidney injury.

A number of studies implicate CRP as an important mediator in the generation of atheromatous coronary plaque, including uptake of low-density lipoprotein by macrophages, triggering increased expression of endothelial cell surface adhesion molecules, and activating complement system proteins.[24,25] Moreover, although there is strong evidence that putative CRP gene single nucleotide polymorphisms influence systemic CRP levels, an independent association between these CRP single nucleotide polymorphisms and adverse cardiovascular events has not been definitively established[26]. Confirmation of a direct causal relationship between post-operative hs-CRP and cardiovascular outcomes will require further investigation.

Another intra-operative factor that is significantly associated with MACCE is peri-operative RBC transfusion. Transfusion of red blood cells remained an independent risk factor of combined cardiovascular event after CABG surgery.[27] Transfusion of stored RBC can augment inflammation by various mechanisms and that might have been reflected in post-operative CRP levels in our study. Another possible explanation is that significant bleeding requiring RBC transfusion might have caused hypoperfusion which can lead to MACCE. Additionally, intra-operative hypoperfusion triggers inflammatory reactions and consequently increases post-operative serum CRP levels.

Low ejection fraction patients may be limitation and one may argue that the current findings may be not generalized to the contemporary surgical population. Anyway, the pre-operative high sensitivity CRP ≥ *to 1.0 mg/dl* is associated with poor outcome after elective OPCABG surgery in dysfunctional heart.

Conclusion

In this study, author conclude that increased pre-operative hs-CRP > *1.0 mg/dl* predict in hospital cardiac and cerebrovascular mortality and morbidity in low EF patients undergoing CABG. Post-operative increase in hs-CRP may be due to inflammatory response of surgery. But its prognostic value for predicting post-operative morbidity needs further randomised control study. These findings may allow for more objective risk stratification of patients who present for elective surgical coronary revascularization.

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