Circ J 2009; **73:** 872 – 877

Predictive Value of C-Reactive Protein for Major Postoperative Complications Following Off-Pump Coronary Artery Bypass Surgery

— Prospective and Observational Trial —

Dae Hee Kim, MD; Jae Kwang Shim, MD, PhD*,#; Seong Wook Hong, MD*; Kwang Rae Cho, MD*; Seung Youn Kang, MD*; Young Lan Kwak, MD, PhD*,#

Background: To prospectively investigate the predictive value of the preoperative C-reactive protein (CRP) concentration for major postoperative complications following off-pump coronary artery bypass (OPCAB) surgery.

Methods and Results: From January 2007 to December 2007, 185 consecutive patients scheduled for elective OPCAB surgery were allocated to a low-CRP group (n=137, CRP <0.3 mg/dl) and a high-CRP group (n=48, CRP ≥0.3 mg/dl). The incidence of major postoperative complications, defined as postoperative myocardial infarction, and 5 major morbidity endpoints including permanent stroke, renal dysfunction, any cardiac surgery reoperation, ventilation for more than 48 h, and deep sternal wound infection were assessed and compared. Multivariate logistic regression was used to determine the predictors of major postoperative complications. Patients in the high-CRP group had a significantly higher overall incidence of major postoperative complications, particularly renal dysfunction. In the multivariate logistic regression model, adjusting all the significant univariate predictors, baseline CRP >0.3 mg/dl and preoperative chronic renal failure (CRF) remained as significant independent predictors of major postoperative complications.

Conclusions: Elevated preoperative CRP level and/or preoperative CRF indicate increased risk of developing major postoperative complications, particularly acute postoperative renal dysfunction in patients undergoing OPCAB surgery. (*Circ J* 2009; **73:** 872 – 877)

Key Words: C-reactive protein; Off-pump coronary artery bypass surgery; Postoperative morbidity

After cardiac surgery, the inflammatory reaction plays a pivotal role in the development of postoperative morbidity and mortality.[1,2] Accordingly, the preoperative inflammatory status of the patient will significantly affect the degree of systemic inflammation and the postoperative outcome.[3,4] Among the biomarkers of inflammatory status, C-reactive protein (CRP) is the most widely used.[5] Numerous studies have incontrovertibly demonstrated the strong predictive value of high-sensitivity CRP (hsCRP) for adverse cardiac events in patients undergoing percutaneous coronary intervention (PCI) and with myocardial infarction (MI).[6–10] As a result, CRP is rapidly evolving into a stronger risk predictor than other novel risk factors in the setting of coronary ischemia and unstable angina. However, its predictive role and clinical application in patients undergoing coronary artery bypass graft surgery (CABG) remains controversial.[3,4,11–14] Moreover, most of the studies are pertinent to on-pump CABG, and no comprehensive data exist for its predictive value in off-pump coronary artery bypass surgery (OPCAB).

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The regional warm, instead of the global cold, ischemia–reperfusion injury imposed on the myocardium and the avoidance of cardiopulmonary bypass (CPB) in OPCAB would confer a different impact of the degree of inflammatory reaction and, consequently, the postoperative outcome.[15] Thus, in terms of the degree of the inflammatory response and myocardial ischemia, OPCAB would stand between on-pump CABG and PCI, and a more distinct role of the preoperative CRP level is expected in OPCAB patients compared with on-pump CABG. We, therefore, designed a prospective and observational trial to investigate the predictive value of the preoperative hsCRP level for major postoperative complications following OPCAB during the postoperative hospitalization period.

Methods

Patients

A total of 185 consecutive patients scheduled for elective OPCAB from January 2007 to December 2007 were included. Patients were excluded because of emergency or

(Received October 26, 2008; revised manuscript received November 22, 2008; accepted December 11, 2008; released online March 13, 2009)

*Department of Anesthesiology and Pain Medicine, Ajou University College of Medicine, Suwon, *Department of Anesthesiology and Pain Medicine and #Anesthesia and Pain Research Institute, Yonsei University College of Medicine, Seoul, South Korea*

Mailing address: Young Lan Kwak, MD, PhD, Department of Anesthesiology and Pain Medicine and Anesthesia and Pain Research Institute, Yonsei University College of Medicine, 134 Shinchon-Dong, Seodaemun-Ku, Seoul 120-752, South Korea. E-mail: ylkwak@yuhs.ac

Table 1. Baseline and Intraoperative Characteristics of the Patients

	Low-CRP (n=137)	High-CRP (n=48)	P value
Age (years)	64.0±8.7	66.9±7.3	0.037
Sex (M/F)	98/39	36/12	0.644
Body surface area (m^2)	1.71±0.17	1.70±0.16	0.734
History			
Hypertension	98 (72)	31 (65)	0.367
Diabetes mellitus	52 (40)	17 (35)	0.754
CRF	10 (7)	5 (10)	0.542
CVA	7 (5)	5 (10)	0.304
PAD	15 (11)	3 (6)	0.412
Previous MI	39 (28)	15 (31)	0.715
Creatinine (mg/dl)	1.1±0.5	1.2±1.1	0.320
NYHA class ≥3	48 (35)	19 (40)	0.573
Preoperative medications			
Nitrate	56 (41)	22 (46)	0.549
β-blockers	105 (77)	36 (75)	0.818
ACEI	24 (18)	14 (29)	0.086
ARB	37 (27)	11 (23)	0.578
CCB	78 (57)	24 (50)	0.406
Aspirin	101 (74)	30 (63)	0.141
Clopidogrel	92 (67)	26 (54)	0.107
Statins	97 (71)	33 (69)	0.789
LVEF (%)	59±12	57±12	0.500
Coronary artery disease			
Left main	6 (4)	1 (2)	0.679
3-vessel disease	109 (80)	40 (83)	0.570
No. of anastomoses	3.3±0.7	3.3±0.7	0.609
Duration of operation (min)	272±72	259±69	0.273

Values are mean ± SD or number of patients (%).
CRP, C-reactive protein; CRF, chronic renal failure; CVA, cerebrovascular accident; PAD, peripheral artery obstructive disease; MI, myocardial infarction; NYHA class, New York Heart Association functional class; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CCB, calcium-channel blocker; LVEF, left ventricular ejection fraction.

urgent surgery, recent MI within the 1 month of the time of enrolment, age under 20 years, known malignancy, active infection, autoimmune disease, or chronic anti-inflammatory therapy other than low-dose aspirin. The study was conducted according to the principles of the Declaration of Helsinki, and written informed consent was given by all patients. The institutional ethics committee approved the study.

The following preoperative data were prospectively collected: age, sex, body surface area, serum creatinine level, left ventricular ejection fraction (LVEF) and medications. Assessment of comorbidities included history of hypertension, diabetes mellitus under medical treatment, neurologic events, chronic renal failure (CRF defined as estimated glomerular filtration rate <60 $ml \cdot min^{-1} \cdot 1.73\,m^{-2}$), vascular disease, and documented history of prior MI.

Anesthetic Management and Operative Technique

All patients received standardized anesthetic management. In the operating room, leads II and V_5 of the ECG and arterial blood pressure were continuously monitored. A thermodilution pulmonary artery catheter was inserted for continuous monitoring of cardiac output and mixed venous oxygen saturation. Anesthesia was induced with intravenous midazolam (0.03–0.07 mg/kg), sufentanil (1.5–3.0 μg/kg) and rocuronium bromide 50 mg, and maintained with sevoflurane (0.8–1.5 vol%) and continuous infusion of sufentanil (0.5–1.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$).

All surgical procedures were performed by the same surgeon through a median sternotomy. To avoid instrumentation of the ascending aorta, a "no-touch" technique[16] was used whenever possible. With this technique, revascularization was carried out using 1 or both internal thoracic arteries connected with an additional graft (mainly the radial artery, and/or saphenous vein) in a Y configuration. To expose and stabilize the target coronary vessel, a deep pericardial suture and suction stabilizer (Rosta® 2.0, Yoorim Corporation, Chungbuck, Korea) was used. During distal anastomosis, mean systemic arterial pressure was maintained within 70–80 mmHg either with a 10–20° Trendelenburg's position and/or norepinephrine infusion. The number of distal anastomoses and operation time were recorded. All patients were transferred to the intensive care unit (ICU) after operation.

Biochemistry

hsCRP was measured by the high-sensitivity nephelometric method (Dade Behring Marburg GMBH, Marburg, Germany) on the morning of the day before surgery, and on the morning of the 1^{st}, 2^{nd}, and 3^{rd} postoperative days (POD 1, 2 and 3). The lower detection limit of this method was <0.015 mg/dl. Creatine kinase-myocardial band (CK-MB) and troponin-T (Tn-T) levels were also measured at the same time points. According to the baseline level of hsCRP, patients were allocated to a low-CRP group, which included patients with hsCRP level <0.3 mg/dl (n=137), and a high-CRP group, which included patients with hsCRP level ≥0.3 mg/dl (n=48). The cut-off point of 0.3 mg/dl was based on the American Heart Association and Centers for Disease Control and Prevention scientific statement suggesting that levels greater than 0.3 mg/dl be considered high.[17]

Postoperative Evaluation

The postoperative clinical course of all patients, including the duration of mechanical ventilation, re-intubation rate, chest tube drainage for 72 h, transfusion requirement, use of inotropic agents or vasopressors, new onset of atrial fibril-

Table 2. Postoperative Outcome Variables

	Low-CRP (n=137)	High-CRP (n=48)	P value
Duration of ventilatory care (h)	15.8±22.6	15.6±9.5	0.950
Re-intubation	5 (4)	1 (2)	1.000
Chest tube drainage (ml)	1,538±584	1,509±636	0.772
Transfusion	56 (41)	16 (33)	0.356
Inotropic agent support	17 (12)	7 (15)	0.700
Vasopressor support	18 (13)	4 (8)	0.376
Atrial fibrillation	23 (17)	12 (25)	0.211
Major postoperative complications	14 (10)	14 (29)	0.002
Postoperative MI	6 (4)	5 (10)	0.160
5-major STS morbidity endpoints	9 (7)	10 (21)	0.010
Stroke	1 (1)	0	1.000
Cardiac reoperation	1 (1)	2 (4)	0.166
Deep sternal infection	1 (1)	0	1.000
Renal dysfunction	4 (3)	7 (15)	0.008
Ventilator care >48 h	4 (3)	1 (2)	1.000
Length of ICU stay (days)	2.3±1.2	2.5±1.7	0.427
Length of postoperative hospital stay (days)	10.4±9.9	11.4±8.2	0.563
Mortality	2 (1)	0	1.000

Values are mean±SD or number of patients (%).
Inotropic agents, dobutamine or milrinone infusion; Vasopressors, norepinephrine >0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or vasopressin infusion; STS, the Society of Thoracic Surgeons; ICU, intensive care unit. Other abbreviations see in Table 1.

lation, and postoperative MI and the 5 major morbidity endpoints were recorded until hospital discharge. The length of stay in the ICU and the postoperative hospitalization, as well as the in-hospital mortality, were also recorded. MI was defined as the occurrence of an increase in CK-MB ≥25ng/dl (5-fold above the upper normal limit) and/or development of new pathologic Q wave on electrocardiography. The 5 major morbidity endpoints were defined as permanent stroke, renal dysfunction, any cardiac surgery reoperation, ventilation >48 h, and deep sternal wound infection.[18] For clarification, renal dysfunction was defined as acute postoperative renal insufficiency resulting in 1 or more of the following: (1) increase of serum creatinine to >2.0 mg/dl, (2) ≥50% increase in creatinine over baseline preoperative value, or (3) new requirement for dialysis. In-hospital mortality was defined as death within the same hospital admission regardless of cause.

Statistical Analysis

Data are expressed as mean±standard deviation or number of patients (%) and were analyzed with SPSS (version 13, SPSS Inc, Chicago, IL, USA). The primary objective of this study was to compare the overall incidence of the major postoperative complications defined as postoperative MI and 5 major morbidity endpoints between groups, and to analyze the predictive value of hsCRP. To compare the low- and high-CRP groups, chi-square or Fisher's exact test for categorical variables and unpaired t-test or Mann-Whitney U test for continuous variables were used as appropriate. To determine the predictive value of hsCRP and other preoperative variables for major postoperative complications, multivariate analysis was used with logistic regression using a forward stepwise selection method. Preoperative variables of P<0.2 in the univariate analysis were included in the regression model. A P-value <0.05 was considered statistically significant.

Results

Patients

OPCAB was successfully performed in all patients without emergency conversion to on-pump CABG. Patients' characteristics and operative data, including the number of grafts performed, were similar between the groups except for age (**Table 1**).

Postoperative outcome variables are shown in **Table 2**. The overall incidence of the predefined major postoperative complications was significantly higher in the high-CRP group. Other postoperative outcome variables were comparable between the groups. Among the predefined major postoperative complications, the overall incidence of the 5 major morbidity endpoints was significantly higher in the high-CRP group, although the incidence of postoperative MI was also higher in the high-CRP group without statistical significance (10% vs 4%, P=0.160). When comparing each parameter constituting the 5 major morbidity endpoints, only the incidence of renal dysfunction was significantly higher in the high-CRP group. Of the patients who developed renal dysfunction, 1 in the high-CRP group required hemodialysis. The creatinine levels returned to preoperative values in all patients before hospital discharge. Both the length of ICU stay and postoperative hospitalization were similar between the groups. The in-hospital mortality rate was also without statistical significance, and the cause of death of 2 patients in the low-CRP group was graft failure and subsequent cardiac arrest, respectively.

Biomarkers

Although the baseline hsCRP levels were essentially different, postoperative CRP showed no differences, peaking on POD 2 in both groups. The white blood cell (WBC) count was significantly higher in the high-CRP group on POD 2. There were no significant differences in the CK-MB and Tn-T levels at baseline or on PODs 1–3 (**Table 3**).

Multivariate Logistic Regression

To determine the risk factors for major postoperative complications, suspected univariate predictors (all perioperative variables shown in **Table 1** and baseline CRP, WBC count, CK-MB, and Tn-T) were assessed, and significant univariate predictors included lower LVEF, history of MI, CRF, cerebrovascular accident, and baseline hsCRP

Table 3. Perioperative Values of Cardiac and Inflammatory Biomarkers

	Low-CRP (n=137)	High-CRP (n=48)	P value
CRP (mg/dl)			
Preoperative	0.097±0.074	1.146±1.048	<0.001
POD 1	6.840±2.641	7.572±2.694	0.106
POD 2	16.184±8.460	16.481±6.437	0.844
POD 3	12.060±4.941	13.717±5.499	0.221
WBC ($10^3/\mu l$)			
Preoperative	7.1±1.8	7.7±2.4	0.100
POD 1	11.1±2.8	11.7±3.7	0.352
POD 2	10.6±3.5	12.1±4.2	0.020
POD 3	9.1±2.9	9.7±2.7	0.205
CK-MB (ng/ml)			
Preoperative	3.33±1.60	4.44±6.39	0.306
POD 1	9.76±9.45	11.12±8.94	0.388
POD 2	7.76±5.75	7.05±4.15	0.474
POD 3	4.43±2.25	4.52±2.16	0.882
Tn-T (ng/ml)			
Preoperative	0.017±0.074	0.097±0.324	0.151
POD 1	0.140±0.161	0.441±1.564	0.209
POD 2	0.160±0.302	0.467±1.521	0.223
POD 3	0.171±0.335	0.214±0.349	0.651

Values are mean ± SD.
POD, postoperative day; WBC, white blood cell count; CK-MB, creatine kinase-MB; TnT, troponin T. Other abbreviation see in Table 1.

Table 4. Univariate and Multivariate Preoperative Predictors of Major Postoperative Complications

Predictors	Univariate P value	Multivariate OR (95%CI)	P value
LVEF	0.156		
History of previous MI	0.029		
Preoperative CRF	0.002	6.163 (1.913–19.855)	0.002
Preoperative CVA	0.088		
Preoperative CRP >0.3 mg/dl	0.002	3.833 (1.602–9.172)	0.003

OR, odds ratio; CI, confidence interval. Other abbreviations see in Table 1.

>0.3 mg/dl. In the multivariate logistic regression model, adjusting all the significant univariate predictors, preoperative CRF and baseline hsCRP >0.3 mg/dl remained significant independent predictors of postoperative major complications (**Table 4**).

When the predictive value of the same risk factors for the development of postoperative renal dysfunction alone were analyzed in a multivariate logistic regression model, preoperative CRF (odds ratio (OR) [95% confidence interval (CI)], 10.173 [2.012–51.440]) and elevated preoperative CRP level (OR [95%CI], 4.883 [1.168–20.410]) were also identified as significant independent predictors with higher OR.

Discussion

In the current study addressing the predictive value of the CRP level for a patient's short-term prognosis following OPCAB, we found that the overall incidence of major postoperative complications was significantly higher in the high-CRP group. Among the postoperative complications, the incidence of renal dysfunction was significantly higher, and the incidences of MI and cardiac reoperation showed a trend toward being higher in the high-CRP group. Furthermore, high preoperative hsCRP level and history of CRF were independent risk factors for the development of major postoperative complications, especially acute postoperative renal dysfunction.

Identification of factors related to an increased risk of postoperative complications allows accurate risk stratification, and provides the rationale for optimizing certain medical conditions of the patient before the surgery, if possible. During the past decade, CRP has emerged as a significant predictor of cardiovascular events in both healthy subjects and patients with coronary artery disease, with consistent clinical evidence.[6–10] Furthermore, the CRP level has been shown to be an independent predictor of future cardiovascular events, adding prognostic information to the Framingham Risk Score, to lipid screening, and to the metabolic syndrome.[19] Thus, in the area of primary prevention, the usefulness of the criterion encompassing the CRP modified ischemic heart disease risk score for global risk prediction is being increasingly recognized.[20]

Cardiac surgery, particularly if requiring CPB, invariably produces a broad and intense systemic inflammatory response to a different extent among individual patients.[21] This systemic inflammatory response, together with microembolization, is being held responsible for the development of most of the morbidities following cardiac surgery, and not surprisingly, the preoperative inflammatory status of the patient significantly affects the degree of systemic inflammatory response during cardiac surgery. However, unlike in the setting of coronary artery disease or PCI, the reported predictive value of the preoperative CRP level for postoperative outcome in on-pump CABG has been controversial.[3,4,11–14] Strong associations between an elevated hsCRP level with an increased overall incidence of infection and sepsis, short- and long-term postoperative mortality, and early graft occlusion has been demonstrated by previous studies.[3,12,14,22] In contrast, a preoperative level of CRP as high as >5 mg/L could not predict in-hospital postoperative complications following primary isolated on-pump CABG.[4] In a prospective study, Tn-T but not CRP was identified as a predictive variable for short-term prognosis following on-pump CABG and those authors suggested that myocardial ischemia plays the main role in on-pump CABG, in contrast with PCI where inflammation is the cornerstone.[23]

OPCAB is associated with a reduced inflammatory reaction and myocardial injury because it avoids the use of CPB and does not impose a global cold myocardial ischemia, but there is still a significant acute inflammatory response as a result of surgical trauma and warm regional myocardial ischemia.[15] In terms of the extent of both the inflammatory reaction and myocardial ischemia, we consider that the effect of OPCAB is between that of on-pump CABG and PCI. Therefore, the prognostic importance of CRP for the patient's outcome would be more definite in OPCAB than in on-pump CABG, although evidence to prove this hypothesis is lacking to date.

As our results indicate, a high preoperative hsCRP level was associated with frequent development of major postoperative complications, especially renal dysfunction. In addition, a high hsCRP, together with preoperative CRF, was identified as an independent predictor for major postoperative complications in our multivariate analysis. Postoperative MI and the 5 major morbidity endpoints are well known as affecting patients' quality of life and may often pose a serious threat to a patient's long-term survival and overall wellbeing after the operation.[18]

Of interest is that when comparing each parameter constituting the major postoperative complications, only the incidence of renal dysfunction was significantly higher in the high-CRP group. Moreover, together with preoperative CRF, an elevated preoperative CRP level was an independent risk factor for postoperative renal dysfunction, in particular, on our multivariate logistic regression analysis. Preexisting renal impairment has been consistently identified as a major predictor for postoperative renal failure in OPCAB.[24,25] However, although not surprising, this strong association of an elevated preoperative hsCRP level with the development of postoperative renal dysfunction following OPCAB is a novel finding of this study. Renal dysfunction after cardiac surgery is well known as having a significant influence on postoperative morbidity and mortality, and although the causes of renal dysfunction after cardiac surgery are multifactorial, the inflammatory response is 1 of the important contributors.[26] In support of the association between elevated preoperative hsCRP level and renal dysfunction, the preoperative inflammatory status as measured by the hsCRP level was closely associated with the postoperative inflammatory reaction and has been shown to magnify the effects of intraoperative inflammatory stressors.[13,14] Moreover, renal filtration contributes to the clearance of many inflammatory cytokines and thus postoperative renal dysfunction per se may also influence the course and magnitude of the inflammatory response, thereby effecting other major complications, including aggravation of the already present renal dysfunction.[27] Based on these perspectives and our results, therapeutic efforts should be made to attenuate the inflammatory response and/or to protect the kidney in patients with an elevated preoperative hsCRP level presenting for OPCAB. For that purpose, statin therapy could be a promising therapeutic strategy, as those drugs have been shown to reduce the levels of certain inflammatory markers, such as hsCRP and IL-6, and to dramatically reduce morbidity and mortality in patients with established cardiovascular disease.[28–30] However, the efficacy of statins in reducing major postoperative complications in patients undergoing OPCAB remains to be proven.

Study Limitations

hsCRP is a well-established marker of inflammation, and despite the preoperative difference in the hsCRP levels and the theory of accentuated inflammatory response in patients with increased baseline inflammatory status, the postoperative hsCRP levels were similar between the groups in this study. Therefore, the suggestion that an increased inflammatory response resulted in the increased incidence of major postoperative complications in the high-CRP group may not seem reasonable. However, hsCRP is only 1 of many inflammatory markers, and thus judging the patient's inflammatory response solely by the serum level of CRP may not be acceptable. The finding that leukocytosis was more pronounced in the high-CRP group on POD 2 also implies that there was an increased inflammatory response in the high-CRP group. Moreover, the fact that a preoperative elevated hsCRP level was an independent predictor of major postoperative complications, despite the similarity in the postoperative hsCRP levels, further strengthens the predictive value of hsCRP.

In conclusion, we found a strong association between an elevated preoperative hsCRP level and the occurrence of major postoperative complications following OPCAB. Furthermore, together with preoperative CRF, a preoperative level of CRP >0.3 mg/dl was an independent risk factor for the development of postoperative major complications, particularly renal dysfunction.

Acknowledgment

We thank Dr Kyung-Jong Yoo (Department of Thoracic and Cardiovascular Surgery, Yonsei University College of Medicine) who performed the OPCAB in this study.

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