Preoperative C-Reactive Protein Predicts Respiratory Infection after Coronary Artery Bypass Graft Surgery

Agda Mezzomo, Odemir Luiz Bordin Junior, Vera Lúcia Portal
Instituto de Cardiologia do Rio Grande do Sul - Fundação Universitária de Cardiologia (IC/FUC), Porto Alegre, RS, Brazil

Abstract

Background: Increased levels of high-sensitive C-reactive protein (hsCRP) in the preoperative evaluation for coronary artery bypass graft surgery (CABG) have been associated to poor outcomes in the postoperative period.

Objective: To evaluate the association of high levels of hsCRP with short-term outcomes after cardiac surgery.

Methods: Prospective cohort with 331 patients who underwent CABG surgery with cardiopulmonary bypass (CPB) at our Institution. Patients were assigned to two groups according to hsCRP levels, measured before surgery: normal (N group) with < 3 mg/L hsCRP; and increased (A group) with ≥ 3 mg/L hsCRP. This cutoff of 3 mg/L had a sensitivity and specificity of 60% for predicting respiratory infection, with a power of 90%. The patients were followed-up during the in-hospital period.

Results: The mean age was 60 years, and 71.6% of the patients were male. HsCRP was increased (group A) in 144 patients (43.5%). In-hospital mortality was 4.8% and the most frequent complications in both groups were: overall infections (18%), respiratory infections (16%), atrial fibrillation (15%) and acute myocardial infarction (7.6%). The incidence of postoperative overall infections was 14.4% in the N group and 23.6% in the A group (P=0.046). Respiratory infections were also more frequent in the A group (21.5% vs. 11.8%; p = 0.024). Multivariate analyses showed that hsCRP level represented an independent predictor of postoperative respiratory infection (OR=2.08, 95% IC = 1.14-3.79).

Conclusions: High preoperative hsCRP level is an independent predictor of respiratory infections in the short-term postoperative period of elective coronary artery bypass graft surgery. (Arq Bras Cardiol 2011;97(5):365-371)

Keywords: Respiratory infection, c-reactive protein, inflammation, coronary artery bypass graft

Introduction

Coronary artery disease (CAD) is the most frequent cause of death and hospitalization in the Western world[1]. Cardiovascular diseases were responsible for 34.2% of deaths in the United States compared to 2006[2], which is similar to what was described in Brazil[3].

Inflammatory processes have been shown to play a role in all aspects of acute coronary syndrome, from the pathogenesis of atherosclerosis to plaque rupture and death of myocardial cells. In each of these stages, infiltration of the cardiovascular tissue with inflammatory cells, controlled by cytokines and adhesion molecules, is evident. Furthermore, soluble markers of inflammation are present in different stages of CAD, and can be used to predict subsequent cardiovascular events[4].

Several inflammatory markers are associated with heart disease. Among them, high-sensitive C-reactive protein (hsCRP) seems to be most significantly associated with cardiovascular events. In healthy individuals, hsCRP is recognized as a predictor of mortality and first-ever myocardial infarction[5-7]. Elevation of this marker is also associated with a worse prognosis in patients with acute myocardial infarction (AMI)[8-10] or undergoing angioplasty[11,12].

Some studies have shown that increased preoperative levels of hsCRP are associated with adverse events after coronary artery bypass graft surgery[13-16], whereas others do not find such association[17]. The main complications in the early postoperative period which are directly associated with increased preoperative levels of hsCRP are not clearly known.

The main objective of this study was to investigate the association of high hsCRP levels in the preoperative period with complications in the early postoperative period of coronary artery bypass graft (CABG) surgery, identifying complications associated with increased hsCRP levels.

Mailing Address: Vera Lucia Portal •
Av. Princesa Isabel, 370- Santana – CEP 90620-000 – Porto Alegre, RS - Brazil
E-mail: veraportal@cardiol.br, verap.pesquisa@cardiologia.org.br, vera.portal@hotmail.com
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Methods

Population

The sample comprised patients of both genders, aged between 20 and 80, undergoing elective CABG with cardiopulmonary bypass at the Institute of Cardiology of RGS, with hsCRP levels measured preoperatively. Exclusion criteria included indication for emergency surgery, unstable angina and recent AMI (less than three months), creatinine higher than 2.0 mg/dl, severe chronic obstructive pulmonary disease (COPD) (predicted FEV1 — forced expiratory volume — <40%), presence of active infection, current use of non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids, class IV congestive heart failure (CHF) or EF < 30%, malignancy or immunosuppressive diseases, recent cerebroencephalic accident (CEA) (less than 1 year), collagen diseases and coagulation disorders.

Study

Initially, patients were evaluated in the preoperative period, where they were presented with the research protocol and signed the Informed Consent (register number 3809/06). The research protocol included, among other variables, the clinical characteristics of patients, the risk factors for cardiovascular disease, medical history and medications used. The study data were recorded, and the protocol was previously approved by the Ethics Committee of the Institution.

A complete physical examination was subsequently performed, and blood samples were collected for laboratory tests (fasting glucose, blood count, platelets, prothrombin time, activated partial thromboplastin time (APTT), anti-HIV (anti-human immunodeficiency virus), urea, creatinine, sodium, potassium, blood gas analysis and qualitative urine test). The levels of hsCRP were determined in the same blood sample by nephelometry (Dade Behring nephelometry), and the time between blood collection and surgery did not exceed three days. Patients were followed during hospitalization, at the intraoperative, immediate postoperative (until 48 h) and early postoperative (48 hours until discharge) periods, to record any complications arising from surgery.

The clinical outcomes analyzed were death, myocardial infarction during and after surgery (diagnosis confirmed by two of the following events: presence of new Q wave in two or more leads of the electrocardiogram; increase of creatine phosphokinase (CK), or of the isoenzyme CK-MB four times above the normal limit; or new segmental cardiomyopathy with akinesia shown by echocardiography); infections in general (endocarditis, urinary infection, surgical wound and mediastinitis); respiratory infection (presence of productive cough and nasal purulent discharge, chest radiation with or without consolidation, and leukocyte counts higher than 10,000/μl); CEA (diagnosed by clinical examination with partial or total paralysis, or sensory depression, and computed tomography with ischemic areas); CHF (cardiac heart failure defined as pulmonary congestion and/or low cardiac output); need for percutaneous coronary intervention (PCI); reoperation; conduction disorder requiring temporary pacemaker; increased bleeding (thoracic drains with blood volumes exceeding 10 ml/kg/h in one hour, 5 ml/kg/h over three consecutive hours or 100 ml/h during four hours); pericarditis (diagnosed by electrocardiogram with ST segment elevation in most leads; pericardial friction rub on cardiac auscultation and/or chest pain); atrial flutter or fibrillation (diagnosed by electrocardiogram).

The group of patients was assigned to two groups according to the level of hsCRP: Group A, with increased hsCRP (≥3 mg/L), included 144 patients; and Group N, with normal hsCRP (<3 mg/L), was composed of the other 187 patients.

Statistical Analysis

The sample size was determined using data on the incidence of complications after CABG, which ranges from 2 to 15% depending on the type of complication. Assuming an incidence greater than 5% for the most frequent complications, a power of 80% and $p \leq 0.05$, the sample size was estimated in 302 patients.

The statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) 17.0. Numerical variables were presented as means and standard deviation, and categorical variables were described as percentages. The Chi-square test was used for categorical variables and the Student's t test for numerical variables.

ANOVA and Kruskal-Wallis tests were used for comparisons between more than two groups (clinical syndromes). $P \leq 0.05$ was considered statistically significant. Associations between increased hsCRP levels and postoperative complications were researched only for those with incidence higher than 4.8%. This cutoff point was defined by analyzing the 4.8% mortality rate observed in our study. We also observed that lower rate outcomes are not statistically significant to be compared to other variables.

Multivariate logistic regression was used to assess independent predictors of postoperative events. Only characteristics with a p value<0.20 in univariate analysis had, or that could increase the risk of respiratory infection (a complication that was associated with CRP in the previous analysis), were submitted to multivariate analysis. The model was used for the following variables: old age, smoking, diabetes mellitus (DM), COPD, obesity, hsCRP and duration of mechanical ventilation.

Results

A total of 331 patients undergoing elective CABG with CPB were evaluated. The average age of patients was 60.92 years, 71.6% of them were male and 93.7% were white. The most prevalent risk factor for ischemic heart disease was hypertension (91.8%), followed by dyslipidemia (68%) and positive family history for ischemic heart disease (61.9%). Among the 331 patients, 144 (43.5%) had increased preoperative hsCRP levels (≥ 3 mg/L).

The analysis of the characteristics presented by the patients during the preoperative period (Table 1) showed that white patients had hsCRP levels lower than those of non-white patients (88.2% versus 97%, $p = 0.001$). Obesity was associated with higher hsCRP (19.4% versus 10.3%, $p = 0.028$). Among patients using statins during the preoperative period,

73.3% had normal hsCRP versus 59.7% with increased hsCRP levels (p = 0.013).

A total of 16 deaths (4.8%) were recorded during hospitalization for myocardial revascularization, considering the transoperative and postoperative periods. As presented in Table 2, complications of higher incidence included respiratory infection (53 cases, 16.0%), atrial fibrillation (51 cases, 15.4%), pericarditis (30 cases, 9.1%) and AMI (26 cases, 7.9%). Infections, particularly of the respiratory tract (Table 3), were significantly more frequent in Group A patients than in the normal hsCRP group (23.6% versus 14.4%, p = 0.046 and 21.5% vs. 11.8%, p = 0.024, respectively) (Figure 1). The association with other variables was not analyzed, due to their low incidence.

The multivariate analysis (Table 4) was adjusted for hsCRP level, smoking, age, DM, obesity, COPD and prolonged postoperative mechanical ventilation (>24 h). Advanced age (>75 years) was an independent risk factor for respiratory infection (OR = 10.43, 95% CI = 3.88 - 28.05). As expected, the same was observed for prolonged mechanical ventilation (>24 h) (OR = 4.84, 95% CI = 2.17 - 10.78). The risk for respiratory infection in the postoperative period was higher for patients with preoperative CRP levels ≥3 mg/L than for individuals with hsCRP levels <3 mg/L (OR = 1.87, 95% CI = 1.0 - 3.49).

When hsCRP levels were analyzed as a continuous variable, the cutoff of 3 mg/L had a sensitivity and specificity of 60% in predicting respiratory infection, with a power of 90%. With a cutoff of 5 mg/L, the sensitivity dropped to 20% and the specificity increased to 80%. Based on these results, we defined the cutoff hsCRP as 3 mg/L, which is similar as in many other studies.

Among the 223 (61.4%) patients who used statins in the preoperative period, hsCRP levels were more frequently lower than 3 mg/L (73.3 vs. 59.7%, p = 0.013). In the multivariate analysis, no association or protective effect was found when major complications (respiratory infection and atrial fibrillation) were considered.

Discussion

This study examined the association of abnormal preoperative hsCRP values (≥3 mg/L) with complications in the early postoperative period in patients undergoing coronary artery bypass grafting. Patients with hsCRP levels above this cutoff point had a higher rate of general infections but a smaller rate of respiratory infection. These results show that hsCRP levels higher than 3 mg/L represented an independent predictor for infections, especially of the respiratory tract, in association with old age and prolonged mechanical ventilation (>24 h). No associations with cardiovascular events, atrial arrhythmias (atrial fibrillation) or death were observed during in this study.

The incidence of respiratory infection in our study was 16%. Respiratory infections have a frequency ranging from 2 to 22% in patients undergoing surgery, with onset on the fourth postoperative day, on average[18]. Ortiz et al[19], in our hospital,

Table 1 - Baseline characteristics of patients according to levels of high-sensitive C-reactive protein (hsCRP)

	hsCRP ≥3 mg/L (144 patients) %(n)	hsCRP <3 mg/L (187 patients) %(n)	p
Mean age	60.44 ± 9.5	61.4 ± 9.2	61.4 ± 9.2
< 65 years	66	64	0.863
65 to 75 years	28	28	
< 75 years	5.6	7.0	
Sex (male)	66.7 (96)	75.4 (41)	0.104
Color (white)	88.2 (127)	97 (183)	0.001
Smoking	31.3 (45)	24.6 (46)	0.222
HBP	91.7 (132)	92 (172)	0.918
Diabetes	34 (49)	32.6 (61)	0.878
Dyslipidemia	61 (93)	71.7 (134)	0.209
FH + IHD	15.3 (22)	19.8 (27)	0.565
COPD	9.7 (14)	4.3 (8)	0.08
Peripheral Vascular Disease	18.8 (27)	12.3 (23)	0.142
Obesity	19.4 (28)	10.3 (19)	0.028
Previous AMI	34.7 (50)	38 (71)	0.622
3-vessel lesion	69.4 (100)	67.9 (127)	0.756
ADA lesion	91 (131)	93.6 (175)	0.496
LMCA lesion	13.2 (19)	12.3 (23)	0.939
Statin use	13.2 (19)	73.3 (137)	0.013

HBP - high blood pressure; FH + IHD - positive family history of ischemic heart disease; COPD - chronic obstructive pulmonary disease; AMI - acute myocardial infarction; ADA - anterior descending artery; LMCA - left main coronary artery.

found a 9.9% incidence of pneumonia in the post-operative period of CABG.

Risk factors, including advanced age, prolonged mechanical ventilation (MV) (>24h), prolonged use of nasogastric tube, preoperative use of H2 receptor blocker or broad-spectrum antibiotics, and transfusion of four units or more of blood concentrate, were evaluated in this study to correct for possible confounding biases. Only one of these factors, prolonged MV (31 cases, 9.36% of the sample), showed higher incidence, representing an independent risk factor for respiratory infection. In the multivariate analysis, however, the hsCRP level remained a risk factor even when adjusted for prolonged VM, although with reduced strength.

Cappabianca et al[20] have investigated an association between increased hsCRP levels (=5 mg/L) and short-term post-CABG complications. A group of 597 patients, presenting either a high (hsCRP ≥ 5 mg/L) or low (hsCRP < 5 mg/L) inflammatory status, was analyzed for infections. Patients in the first group had a higher rate of infections in general and surgical wound, showing that hsCRP levels represent an independent marker. At a mean follow-up of 1.5 years, patients with increased hsCRP levels had also a higher mortality rate. This study showed similar results for early postoperative complications, except for the site of infection[20].

Table 2 - More frequent complications in the postoperative stage

Outcomes	Incidence % (n)
Death	4.8 (16)
AMI	7.6 (26)
CEA	1.2 (4)
Atrial fibrillation	15.4 (51)
Bleeding	7.9 (26)
Reoperation	1.5 (5)
Pericarditis	9.1 (30)
Infections in general	18.4 (60)
- Respiratory infection	16 (53)
- Urinary tract infection	0.6 (2)
- SW infection + mediastinitis	2.7 (9)
Pacemaker	1.2 (4)
CHF	3.6 (12)
Emergency PTCA	0.6 (2)

Incidence of major clinical outcomes in general and in each of the groups (normal and increased CRP). AMI - acute myocardial infarction; CVA - cerebrovascular accident; SW - surgical wound; CHF - congestive heart failure; PTCA - percutaneous transluminal coronary angioplasty.

Table 3 - Most frequent complications in the postoperative period and their relationship with high-sensitive C-reactive protein levels

Outcomes	Incidence % (n)	hsCRP ≥3 mg/L (%)	hsCRP <3 mg/L (%)	p
Death	4.8 (16)	4.2	5.3	0.812
AMI	7.6 (26)	5.6	9.6	0.247
Atrial fibrillation	15.4 (51)	15.3	15.5	0.954
Pericarditis	9.1 (30)	6.9	10.7	0.324
Infections in general	18.4 (60)	23.6	14.4	0.046
Respiratory infection	16 (53)	21.5	11.8	0.024

CRP - C-reactive protein; AMI - acute myocardial infarction.

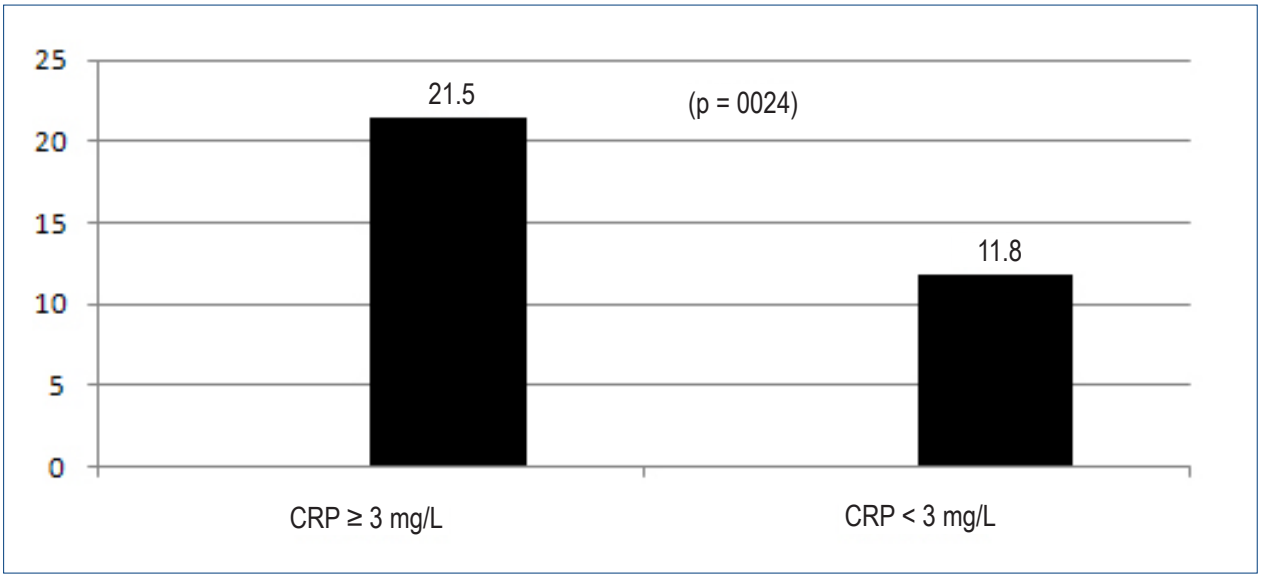

Figure. 1 - *Incidência de infecções em geral e infecção respiratória, de acordo com o nível de proteína C reativa de alta sensibilidade (PCRas).*

Table 4 - Logistic regression for respiratory infection

	RESPIRATORY INFECTION	
	Univariate OR (95% CI)	Multivariate OR (95% CI)
hsCRP ≥3 mg/L	2.06 (1.13-3.74)	2.32 (1.23-4.37)
DM	2.35 (1.06-5.25)	0.59 (0.3-1.17)
Obesity	1.28(0.579-2.84)	
DPOC	2.09 (0.778-5.62)	
Smoking	0.94 (0.48-1.82)	
Age group		
65-75 anos	2.08 (1.075-4.051)	2.14 (1.094-4.192)
> 75 anos	9.18 (3.151-23.967)	10.43 (3.88-28.05)
MV >24 h	4.60 (2.05-9.78)	4.84 (2.17-10.78)

OR - odds ratio; CI - confidence interval; hsCRP - high-sensitive C-reactive protein; DM - diabetes mellitus; COPD - chronic obstructive pulmonary disease; MV - mechanical ventilation.

Inflammation has been widely assessed in the CAD, from the formation of atherosclerotic plaque to its rupture in acute myocardial infarction[21]. The relationship of increased hsCRP with cardiovascular events in healthy individuals is well established[5,6], and other studies are now investigating the association between increased preoperative hsCRP levels and events in the postoperative period of coronary artery bypass grafting. In a study of 113 patients undergoing CABG with cardiopulmonary bypass, Gaudino et al[17] observed that patients with preoperative hsCRP ≥ 5 mg/L had a peak increase of hsCRP on the second day after surgery. However, no association was found between short-term clinical events and inflammatory status[17].

Most studies have focused on evaluating the preoperative inflammatory status as a predictor of events in the postoperative period. In a study with 764 patients undergoing CABG, Biancari et al[13] showed that a value of hsCRP 10 mg/L or more was an independent risk factor for in-hospital mortality, mainly due to cardiac complications. This study poses the question about whether hsCRP is only a marker of severity or may represent a potential target to optimize the preoperative conditions of patients[13]. Another study by the group of Biancari, with 843 patients, evaluated the association of hsCRP levels with long-term post-CABG outcomes. No association was found between increased hsCRP with events in the early postoperative period. A follow-up of 12 years showed a decreased survival rate in these patients[22].

Those studies did not identify specific complications related to increased preoperative hsCRP levels, whereas in this study, the results showed an association with infections, especially of the respiratory tract. One possible explanation for the high rates of infectious complications in patients with an altered inflammatory status during the preoperative period relates to enhanced bacterial growth in the presence of high levels of inflammatory mediators[23,24].

Although long-term evaluation of patients was not considered in this study, it is well known that the risk of mortality and readmission to hospital for cardiovascular causes is directly related to high preoperative levels of hsCRP. In a three-year follow-up (mean time 1.5 years) of cardiac patients, Cappabianca et al[20] found that hsCRP is an independent risk factor for mortality and hospitalization for cardiac complications.

High-sensitive CRP levels, initially considered only as a biological marker, is currently recognized as a mediator of atherosclerosis and a predictor of inflammatory status[25]. Considering this possibility, a major retrospective study has shown that preoperative therapy with statin is associated with a reduction of morbidity and mortality following a CABG procedure[26]. This study showed that statin use was significantly associated with hsCRP levels <3 mg/L, but not with reduction of cardiovascular events in the postoperative stage. A recent study by Vaduganathan et al[27] with 3056 patients observed that statin therapy in the perioperative period was associated with reduced mid-term mortality for patients undergoing cardiac surgery irrespective of their baseline lipid status (HR 0.34; P 0.004)[27]. Another random test evaluated the effect of statin (rosuvastatin) on the patient's inflammatory profile and on the risk of perioperatory myocardial injury. We observed that 58% of the patients using statin showed increased CRP levels, against 88% in the controlled group. These study also demonstrated that pretreatment with statin reduces myocardial damage after coronary surgery and could improve both short- and long-term results[28].

It is important to observe that patients included in this study were clinically stable, since patients with recent acute coronary syndromes (ACS) and/or decompensate CHF and/or recent CEA and/or active infection anywhere in the body were excluded. The importance of increased hsCRP levels as a marker of higher risk for complications, represented here by respiratory infections, is therefore stressed.

One of the limitations of this study was that respiratory secretions were not analyzed by quantitative culture, which may overestimate the incidence of respiratory infections. However, at least two meta-analysis studies have shown that this diagnostic aspect remains controversial[29,30]. Moreover, even though infections were mainly observed, general infection was also positively associated with increased hsCRP levels, suggesting a significant relationship between this marker and infectious complications.

In conclusion, this study showed that altered preoperative hsCRP levels (≥3 mg/L) represent an independent predictor of respiratory infection in the early postoperative period of elective CABG.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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