Pre-operative high sensitive C-reactive protein predicts cardiovascular events after coronary artery bypass grafting surgery: A prospective observational study

Mindaugas Balciunas1,3, Loreta Bagdonaite2, Robertas Samalavicius1, Laimonas Griskevicius4, Alain Vuylsteke5
1Department of Pathology, Forensic Medicine and Pharmacology, 2Department of Physiology, Biochemistry and Laboratory Medicine, Vilnius University Faculty of Medicine, Vilnius, Lithuania, 3Centre of Anaesthesiology, Intensive Therapy and Pain Management, 4Centre of Hematology, Oncology and Transfusion Medicine, Vilnius University Hospital Santariskiu Clinics, Vilnius, Lithuania, 5Department of Anaesthesia and Intensive Care, Papworth Hospital NHS trust, Papworth Everard Cambridge, CB23 3RE, UK.

ABSTRACT

C-reactive protein is a powerful independent predictor of cardiovascular events in patients with coronary artery disease. The relation between C-reactive protein (CRP) concentration and in-hospital outcome, after coronary artery bypass grafting (CABG), has not yet been established. The study aims to evaluate the predictive value of pre-operative CRP for in-hospital cardiovascular events after CABG surgery. High-sensitivity CRP (hs-CRP) levels were measured pre-operatively on the day of surgery in 66 patients scheduled for elective on pump CABG surgery. Post-operative cardiovascular events such as death from cardiovascular causes, ischemic stroke, myocardial damage, myocardial infarction and low output heart failure were recorded. During the first 30 days after surgery, 54 patients were free from observed events and 14 developed the following cardiovascular events: 10 (15%) had myocardial damage, four (6%) had low output heart failure and two (3%) suffered stroke. No patients died during the follow-up period. Serum concentration of hs-CRP ≥ 3.3 mg/l (cut-off point obtained by ROC analysis) was related to higher risk of post-operative cardiovascular events (36% vs 6%, \( P = 0.01 \)) , myocardial damage (24% vs 6%, \( P = 0.04 \)) and low output heart failure (12% vs 0%, \( P = 0.04 \)). Multivariate logistic regression analysis showed that hs-CRP ≥ 3.3 mg/l (\( P = 0.002 \), O.R.: 19.3 (95% confidence interval (CI) 2.9-128.0)), intra-operative transfusion of red blood cells (\( P = 0.04 \), O.R.: 9.9 (95% C.I. 1.1-85.5)) and absence of diuretics in daily antihypertensive treatment (\( P = 0.02 \), O.R.: 15.1 (95% C.I. 1.4-160.6) were independent predictors of combined cardiovascular event. Patients having hs-CRP value greater or equal to 3.3 mg/l pre-operatively have an increased risk of post-operative cardiovascular events after on pump coronary artery bypass grafting surgery.

Key words: C reactive protein, coronary artery bypass grafting surgery, cardiovascular events

INTRODUCTION

Systemic inflammation plays a pivotal role in the development and progression of atherosclerosis.\(^1\) C reactive protein (CRP) has emerged as a marker of atherosclerosis and remained significant in the presence of risk factors such as smoking, hypertension or diabetes.\(^2\) Mainly synthesized in the liver as an acute phase reactant, CRP is also produced in smooth muscle cells within human coronary arteries,\(^3\) and may provide an adjunctive method for assessment of cardiovascular risk.\(^4,5\)

Baseline levels of CRP are strong, independent predictors for future myocardial infarction,
stroke, peripheral vascular disease among healthy individuals without known vascular disease.\[^{6-9}\] Furthermore, levels of CRP have been found to predict recurrent coronary event and death among patients undergoing revascularization procedures.\[^{10-12}\]

Prediction of future cardiovascular events requires quantification of CRP concentrations within reference range below of 3-5 mg/l\[^{6}\] and various high sensitivity CRP assays have been developed.\[^{13}\] The relation between CRP concentration and in-hospital outcome after coronary artery bypass grafting (CABG) has, however, not yet been established. We investigated the predictive value of a pre-operative high sensitivity CRP on in-hospital cardiovascular events after elective CABG surgery.

**MATERIALS AND METHODS**

This study conforms to the principles outlined in the Declaration of Helsinki and was approved by the Lithuanian Bioethical Committee.

**Study population**

Sixty six patients were enrolled in following written informed consent.

Inclusion criteria - patients scheduled for on pump CABG surgery, less than 75 years and with left ventricle ejection fraction greater than 30%.

Exclusion criteria included diabetes mellitus (non-insulin dependent and insulin dependent), chronic obstructive pulmonary disease (documented asthma, chronic bronchitis or pulmonary emphysema), myocardial infarction within 30 days of inclusion in the study, chronic renal disease (glomerular filtration rate less than 56 mL/min/m\(^2\) for male and 50 mL/min/m\(^2\) for female), chronic liver disease (total bilirubin concentration greater than 17 μmol/l), treatment with intravenous nitrates or inotropes before surgery, re-do cardiac surgery, pulmonary hypertension, extra-cardiac arteriopathy or treatment with steroids in the previous six months.

**Angiography**

The number, type and severity of diseased coronary arteries were determined based on angiography of the patient. The left anterior descending, left circumflex, right coronary artery was considered to be diseased if the stenosis was equal or greater than 60% of the luminal diameter. The left main coronary artery was classified to be diseased if stenosis was equal to or greater than 50% of luminal diameter was reported.\[^{14}\]

**Anesthesia and surgery**

All patients underwent general anesthesia according to our standardized protocol. Induction of anesthesia was performed with midazolam, fentanyl, and etomidate. Rocuronium or cisatracurium were used to facilitate tracheal intubation and ensure muscle relaxation throughout the surgery. A mixture of volatile anesthetics (Sevoflurane or Isoflurane), propofol and remifentanil were used for the maintenance of anesthesia. No antifibrinolytic agents were administered.

Surgery was performed during mild hypothermia (32-34°C) with standardized cardiopulmonary bypass (CPB) technique. The extracorporeal circuit was primed with 1000 ml of ringer’s lactate, 500 ml of hydroxyethylstarch 130/0.4 6%, 250 ml of mannitol 15% and 1 g. of cefazolin was also added. A non-pulsatile pump flow was kept between 2.0-2.4 L/min/m\(^2\) to maintain mean arterial pressure between 50 and 70 mmHg. Hydroxyethylstarch 130/0.4 6% and gelatine four per cent were used for volume therapy during and after surgery. Activated clotting time (kaolin as activator) was kept greater than 480 seconds with unfractionated heparin during artificial blood circulation. The heart was arrested using antegrade/retrograde intermittent tepid blood cardioplegia. Following cessation of CPB heparin was neutralized with protamine sulphate to correct the ACT to less than 120 seconds. After skin closure, patients were transferred to the surgical intensive care unit (ICU). Donated red blood cells were transfused if hemoglobin level dropped below 80 g/L during CPB and below 90 g/L after CPB. Transfusion of blood at higher hemoglobin levels as well as infusions of catecholamines was given at the discretion of the attending physician. Blood drained from the thoracic cavity was not re-transfused. Patients were sedated with morphine and propofol by infusion until they fulfilled ventilator weaning criteria according to our protocol. Infusion of epinephrine and/or norepinephrine was gradually discontinued and patients free of inotropic drugs were discharged from ICU.

**Laboratory assays**

Blood for biochemical and complete blood count analysis was taken in the morning on the day of surgery and on the first postoperative day (POD) at 12 hours after surgery in ICU from a peripheral vein using a tourniquet. Creatinine, troponin I, white blood cells (WBC), platelets (PLT), red blood cells (RBC) count and hemoglobin (Hb) levels were measured by certified technician in the central biochemical and clinical laboratory.
A highly sensitive CRP (hs-CRP) analysis was performed using the commercially available Nephelometer system (BN II (Dade Behring, USA) – an automated blood test that uses particle-enhanced immunonephelometry to quantify CRP in serum samples. Polystyrene particles coated with monoclonal antibodies against CRP became agglutinated when mixed with samples containing CRP. The intensity of light scattering due to agglutination reaction was measured using nephelometer and directly related to the concentration of CRP. The lower detection limit is 0.5 mg/l.[15]

Data collection
Demographic and intra-operative data was recorded prospectively, including aortic cross clamp time, CPB time, duration of surgery, number of grafts, intraoperative red blood cell transfusion[16] and lowest esophageal temperature on CPB. Recent myocardial infarction (MI) was defined as myocardial infarction less than 90 days at the time of surgery.[17]

Patients were followed up for 30 days after surgery and events recorded included (1) death from cardiovascular causes,[18] (2) ischemic stroke[18] (defined as new neurologic deficit lasting for at least 24 hours with definite image evidence of cerebro-vascular accident by head computer (tomography). (3) low output heart failure (LOF) (defined as needing one of the following: Intraoperative intra-aortic balloon pump (IABP), return to CPB after initial separation, or ≥ two inotropes at 48 hours post-operatively)[19] (4) myocardial damage (defined as elevated troponin I (Tn I) greater than 10.0 μg/l at 12 hours after surgery)[19] and (5) myocardial infarction (defined as elevated troponin I (Tn I) greater than 10.0 μg/l at 12 hours after surgery associated with characteristic electrocardiographic (ECG) changes or echocardiographically documented new dyskinetic- akinetic segment).[19,20]

Statistics
The normal distribution of continuous variables was checked with one-sample Kolmogorov-Smirnov test. Categorical data are expressed as number (%), continuous variables as mean and standard deviation (mean ± SD) if normally distributed or as median (range) otherwise. The continuous variables and frequencies between groups were compared by Mann-Whitney U test and Chi Square or Fisher exact test as appropriate. In order to evaluate the predictive ability of preoperative hs-CRP on combined postoperative cardiovascular event (death from cardiovascular causes, ischemic stroke, low output heart failure, myocardial damage and myocardial infarction), receiver operating characteristic curve was made and the optimum cut-off value, with the combination of the highest sensitivity and specificity were calculated. Variables that had uni-variate probability value of less than 0.1 or those judged to be clinical important to predict combined postoperative cardiovascular event were included in a logistic regression model with forward stepwise selection. Differences were considered significant at P less than 0.05. Data was analyzed using SPSS Package for Windows version 11.5 (SPSS Inc., Chicago, IL, USA).

RESULTS
During the first 30 days after surgery, 54 patients were free from observed events and 14 developed following cardiovascular events: 10 (15%) had myocardial damage, 4 (6%) had low output heart failure and two (three per cent) suffered stroke. No patients had MI and no patients died during the follow-up period. The impact of pre- and ina-operative clinical variables, according to uni-variate analysis, on combined post-operative cardio-vascular event is shown in Table 1.

Thirty three patients had elevated serum concentration preoperatively of hs-CRP ≥ 3.3 mg/l (P = 0.014; area 0.714 (95% C.I. 0.58-0.85)). The incidence of preoperative level of hs-CRP ≥ 3.3 mg/l was significantly higher among patients with recent MI. Table 2 shows the distribution of other preoperative variables according to high sensitivity CRP less than 3.3 mg/l or ≥ 3.3 mg/l. With preoperative hs-CRP ≥ 3.3 mg/l, the cumulative event incidence was 36% compared to 6% in patients with levels preoperatively of hs-CRP less than 3.3 mg/l (P = 0.01). Patients with concentration preoperatively of hs-CRP greater than or equal 3.3 mg/l had higher risk of myocardial damage (24% vs 6%, P = 0.04) and low output heart failure [12% vs 0%, P = 0.04] after surgery. Multivariate logistic regression included patient’s age, gender, MI, recent MI, pre-operative left ventricle ejection fraction, pre-operative hs-CRP, treatment with diuretics, heparin, calcium blockers and intra-operative red blood cell transfusion. Serum concentration preoperatively of hs-CRP ≥ 3.3 mg/l (P = 0.002, O.R.: 19.3 (95% C.I. 2.9-128.0)), transfusion of red blood cells intra-operatively (P = 0.04, O.R.: 9.9 (95% C.I. 1.1-65.5)) and absence of diuretics in daily antihypertensive treatment (P = 0.02, O.R.: 15.1 (95% C.I. 1.4-160.6) were independent predictors of combined cardiovascular event after CABG surgery.
In this study, elevated pre-operative level of hs-CRP was an independent risk factor of post-operative combined cardiovascular event in patients undergoing CABG surgery.

This is in agreement with previous studies showing that low cardiac output syndrome and cardiac related death occurred more frequently in CABG patients who had a preoperative CRP higher or equal to 10.0 mg/l. A value of pre-operative CRP greater than 5.0 mg/l has been associated in a similar group of patients to an increase in catecholamine support, an increase in in-hospital mortality, and low output heart failure.

In contrast, others have reported that a CRP cut-off at 5.0 mg/l in CABG patients was not associated to an increase incidence of post-operative renal failure, ventilation, duration of inotropic support, blood transfusions, myocardial infarction, need for re-exploration due to surgical bleeding, death and duration of stay in ICU and in hospital.

None of these studies differs used the high sensitivity test for CRP. This may explain the lower cut-off value we are proposing. We identified those patients with hs-CRP ≥ 3.3 mg/l had higher incidence of cumulative cardio-vascular event, higher risk of myocardial damage and low output heart failure.

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Treatement with lipid lowering drugs affects CRP levels, and has been shown to reduce the incidence of death and higher incidence of post-operative infections.
myocardial infarction within 30 days after CABG and the greatest benefit of statins was found among patients with evidence of persistence inflammation.

The number of patients those treated with lipid lowering drugs didn’t differ between groups with and without cardiovascular events, and in agreement with EUROASPIRE study less than half of our patients received statins pre-operatively.

Diuretics, in particular low dose thiazide and thiazide-like diuretics were not superior to ACE-inhibitor in lowering rate of myocardial infarction, stroke or death in patients with isolated systolic hypertension. While others found that thiazide diuretics reduced the incidence of stroke and cardiovascular mortality among hypertensive individuals. In our study fewer patients in cardiovascular events group received diuretics preoperatively, and inclusion of diuretics in antihypertensive therapy was related to lower risk of combined cardiovascular event after cardiac surgery.

Age, recent MI and intra-operative transfusion of red blood cells were risk factors of peri-operative myocardial infarction and low cardiac output syndrome. Patients, suffered from myocardial infarction and low cardiac output syndrome were risk factors of peri-operative effects group received diuretics preoperatively, and inclusion of diuretics in antihypertensive therapy was related to lower risk of combined cardiovascular event after cardiac surgery.

Circulating levels of CRP have been shown to increase in patients suffering from acute MI or chronic heart failure. Others have found elevated CRP levels among obese or diabetic patients and correlation of CRP with age.

In our study, higher number of patients with concentration preoperatively of hs-CRP ≥ 3.3 mg/l had recent MI and we found a positive correlation of hs-CRP with patients’ age (r = 0.3; P = 0.01) and body mass index (r = 0.25; P = 0.04) but the pre-operative hs-CRP remained an independent risk factor of combined cardiovascular event after CABG.

Small sample size is the major limitation of this study. Low operative risk patients is another limitation and one may argue that the current findings may be not generalized to the contemporary surgical population since the risk profile of patients undergoing cardiac surgery is worsening. Anyway, the pre-operative high sensitivity CRP greater or equal to 3.3 mg/l was associated with poor outcome after elective CABG surgery.

We conclude that pre-operative inflammatory state as measured by hs-CRP is an important determinant of post-operative outcome after CABG surgery. This might be used to refine the predictive value of scores such as the Euroscore. Further studies with larger number of patients are needed to allow generalization of our findings.

REFERENCES

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