CLINICAL SCIENCE

C-Reactive protein predicts acute myocardial infarction during high-risk noncardiac and vascular surgery

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BACKGROUND: High-sensitivity C-reactive protein predicts cardiovascular events in a wide range of clinical contexts. However, the role of high-sensitivity C-reactive protein as a predictive marker for perioperative acute myocardial infarction during noncardiac surgery is not yet clear. The present study investigated high-sensitivity C-reactive protein levels as predictors of acute myocardial infarction risk in patients undergoing high-risk noncardiac surgery.

METHODS: This concurrent cohort study included patients aged ≥50 years referred for high-risk noncardiac surgery according to American Heart Association/ACC 2002 criteria. Patients with infections were excluded. Electrocardiograms were performed, and biomarkers (Troponin I or T) and/or total creatine phosphokinase and the MB fraction (CPK-T/MB) were evaluated on the first and fourth days after surgery. Patients were followed until discharge. Baseline high-sensitivity C-reactive protein levels were compared between patients with and without acute myocardial infarction.

RESULTS: A total of 101 patients undergoing noncardiac surgery, including 33 vascular procedures (17 aortic and 16 peripheral artery revascularizations), were studied. Sixty of the patients were men, and their mean age was 66 years. Baseline levels of high-sensitivity C-reactive protein were higher in the group with perioperative acute myocardial infarction than in the group with non-acute myocardial infarction patients (mean 48.02 vs. 4.50, p = 0.005). All five acute myocardial infarction cases occurred in vascular surgery patients *with* high CRP levels.

CONCLUSIONS: Patients undergoing high-risk noncardiac surgery, especially vascular surgery, and presenting elevated baseline high-sensitivity C-reactive protein levels are at increased risk for perioperative acute myocardial infarction.

KEYWORDS: C-reactive protein; Noncardiac surgery; Cardiac risk in noncardiac surgery; Perioperative events; Cardiovascular disease.

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INTRODUCTION

Perioperative acute myocardial infarction (AMI) is seen in less than 2% of patients undergoing noncardiac surgery in nonselected series. In the United States, approximately 27 million patients undergo these procedures annually, and approximately 8 million patients have coronary disease or coronary risk factors.[1] Approximately one million cases of perioperative cardiac complications, and 50,000 cases of AMI are diagnosed annually, with significant morbimortality and medical costs.[2,3]

Atherosclerosis has an inflammatory nature[4,5] and results in thrombotic complications.[6] Inflammatory markers, such as high-sensitivity C-reactive protein (hsCRP), are useful prognostic factors for cardiovascular events in several situations, independent of the traditional risk factors described in the Framingham risk score.[7-13] The guidelines established by the Center for Disease Control and Prevention and the American Heart Association (AHA) in 2003 included hsCRP as a useful tool for therapeutic decision-making in selected cases.[14]

However, few studies have investigated whether hsCRP levels might predict cardiac events in patients undergoing noncardiac surgery,[15] and to this date, scores and guidelines to evaluate risk factors for heart disease do not include the analysis of hsCRP levels.[16-21] In only one report, a prospective cohort study of patients undergoing peripheral vascular surgery, a higher frequency of major cardiac events was observed in patients with elevated hsCRP levels.[22,23]

Thus, the present cohort study was designed to investigate hsCRP levels as predictors of perioperative AMI during high-risk noncardiac surgery.

METHODS

A concurrent cohort study was conducted to test for a possible association between preoperative hsCRP levels and perioperative AMI in patients undergoing high-risk noncardiac surgery. High-risk surgery, as defined by the ACC/AHA 2002 guidelines, includes major, urgent surgeries, particularly in elderly individuals; aortic or other major vascular surgery; peripheral vascular surgery; and/or prolonged surgeries associated with substantial fluid or blood loss.[21] The study was conducted between March 2006 and July 2007 in two large hospitals in Porto Alegre (a state capital in south Brazil) after approval from the Research Ethics Committees of the two institutions. Male and female patients over 50 years of age were included. Patients with infections diagnosed during the previous two weeks and those who had undergone endoscopic and/or video-assisted surgery were excluded from the sample. Nine patients refused to participate in the study, and three other patients were excluded because their surgeries were intraoperatively modified from major to minor procedures. Patients were monitored with clinical follow-up electrocardiogram (ECG) and biomarker and/or cardiac enzyme exams until discharge or until they were considered ready for discharge. The investigators were unaware of preoperative hsCRP levels until the study was concluded.

All patients signed an informed consent form.

Blood collection and laboratory methods

Anamnesis and electrocardiograms were obtained for all patients. Peripheral blood samples were collected for laboratory analyses (including hsCRP levels) at hospital admission, on the day before surgery or immediately before the surgical procedure. During follow-up, levels of troponin I or T and/or total creatine phosphokinase (CK t) or CK-myocardial band (CK-MB) were determined, and ECGs were performed on the first and fourth mornings following surgery. Additional ECGs and enzyme/biomarker analyses were performed if needed. Clinical data were collected daily until discharge.

All ECGs were analyzed by two independent cardiologists. Outcome analysis was performed by adjudicators blinded to the hsCRP status.

The hsCRP concentration in serum or plasma samples was determined by nephelometry in a central laboratory, using standardized procedures and validated methodology. The following reagents were used: VITROS Chemistry Products (Ortho-Clinical Diagnostics, Inc. 100. Indigo Creek Drive; Rochester, NY 14626-5101) hsCRP, 17 VITROS calibrator kit and FS VITROS Calibrator 1. Troponin I or T levels were determined with a validated technique, using the VITROS Troponin I reagent pack. In some cases, the CPK-T and CPK-MB levels were determined by dry chemistry analysis.

Definition of end points

The primary end point was perioperative AMI, defined according to the consensus criteria of the Joint ESC/ACC Committee 2000:[24]

1. Increased Troponin I or T levels or an elevated CKT/CK-MB relationship associated with at least one of the following findings: development of new pathological Q waves, ECG alterations suggestive of ischemia, need for coronary interventions, or ischemic symptoms, or
2. Pathological findings suggestive of AMI.

Secondary end points included noncardiac death, minor outcomes (including acute atrial fibrillation, acute decompensation of cardiac heart failure (HF), bronchopneumonia, acute renal failure, thromboembolic events and infection/dehiscence of the surgical wound), and length of hospital stay.

Statistical analysis

SPSS v15.0 software was used for the analyses. Quantitative variables are presented as means and standard deviations or medians and interquartile intervals. Categorical variables are presented as proportions with 95% confidence intervals. The Mann-Whitney test was used to evaluate differences in CRP levels between patients with events and those without. In addition, ROC curves were used to determine the best CRP cutoffs that predicted events. Categorical variables were analyzed using the chi-squared test, and the relationship between CRP levels and length of hospital stay was evaluated with the Spearman correlation. For all analyses, results were considered significant if $p<0.05$.

Concentrations of hsCRP, gender, age and the Cardiac Risk Index for major surgery (CRI) (20) were included in a forward stepwise multivariable logistic regression model.

RESULTS

The characteristics and risk profiles of the 101 patients (60 men) included in the study are presented in Table 1. The patients' mean age was 66 years.

Surgical procedures (n = 101) included 33 vascular (17 aortic and 16 peripheral artery revascularizations), 29 orthopedic, 33 abdominal (including three cases of liver transplantation), three thoracic and three neurological

Table 1 - Baseline characteristics of the study population.

Characteristic	N (%)
Age (mean ± SD)	66±59
Males (n, %)	60 (59.4)
Type of surgery (n, %)	
Peripheral vascular	16 (15.8)
Aortic	17 (16.8)
Orthopedic	29 (28.7)
Abdominal	33 (32.6)
Thoracic	3 (2.9)
Neurological	3 (2.9)
CD history (n, %)	25 (24.7)
Cerebrovascular disease history (n, %)	12 (11.88)
DM/insulin history (n, %)	11 (10.89)
HF history (n, %)	11 (10.89)
CRF (creatinine >2) (n, %)	7 (6.93)
Statin use (n, %)	36 (35.6)
Beta-blocker use (n, %)	51 (50.5)
Length of surgery (min) (mean ± SD)	297.6 (285±105.2)
Length of hospital stay (days) (median ± IQI 25-75)	8 (7-15)

CD: coronary disease; DM: diabetes mellitus; HF: heart failure; CRF: chronic renal failure; IQI: interquartile interval.

Table 2 - Median and quartiles of CRP levels in the groups with and without events

		hsCRP (median, Q1-Q3)	P
AMI (n = 5)	Yes	48.02 (14.02-230.12)	0.005
	No	4.50 (2.24-16.83)	
Noncardiac death (n = 6)	Yes	2.91 (1.72-5.11)	0.130
	No	5.58 (2.33-20.96)	
Minor outcomes (n = 39)*	Yes	7.59 (2.63-38.29)	0.076
	No	4.50 (2.00-13.42)	

AMI: acute myocardial infarction; Q_1; first quartile; Q_3: third quartile; hsCRP: high-sensitivity C-reactive protein.
*Minor outcomes: atrial fibrillation, acute heart failure, surgical wound infection, bronchopneumonia, thromboembolic events.

interventions. Two surgeries were urgent (both for ruptured aortic aneurisms).

Baseline hsCRP levels in the groups with and without outcomes are presented in Table 2. Median hsCRP levels were 48.02 (14.02-230.12) and 4.50 (2.24-16.83) in patients with and without AMI, respectively (p = 0.005). Ten patients showed hsCRP levels above 100 mg/L. Of these patients, two had major events during follow-up (20%), compared with 3.3% in the group with hsCRP levels <100 mg/L (p = 0.075).

All five AMI cases occurred in vascular surgery patients *with* high CRP levels. When examining only vascular surgery patients, the association between CRP levels and AMI remained significant (p = 0.018). During logistic regression, the CRP level remained significant (OR 12.1 p = 0.025), but vascular surgery showed marginal significance (OR = 5.6, p = 0.05).

High sensitivity CRP levels were similar in the group of patients with noncardiac deaths and those without, as well as for minor outcomes (p >0.05) (Table 2).

A positive, statistically significant relationship was observed between hsCRP levels greater than 10 mg/L and longer hospital stay compared with patients with levels under 10 mg/L (r = 0.32 and p = 0.001).

Table 3 presents the relative and absolute risks according to hsCRP levels <10 mg/L and ≥10 mg/L, as well as diagnostic properties based on this cut-off point. High sensitivity CRP's sensitivity for predicting perioperative AMI was 100%, with high specificity (68%) and a high negative predictive value (>99%).

No associations were observed between perioperative AMI incidence and gender or use of beta-blockers and/or statins. Additionally, hsCRP levels did not differ according to beta-blocker/statins use or CRI (20).

In the bivariable analysis, CRI was significantly associated with the incidence of AMI (p = 0.028 for linear association). In the multivariable logistic regression analysis, however, hsCRP levels ≥10 remained the only independent predictors of perioperative AMI (RC 14.27, p = 0.017) after adjusting for CRI, gender and age. Table 4 shows the odds ratios of MACE for patients with hsCRP levels ≥10, adjusted by CRI. The results were reanalyzed after excluding 10 patients with suspected collagenosis, recent fever, bleeding for more than one day, invasive neoplasia or toe necrosis; all of these patients had hsCRP levels >100 mg/L. However, the results were similar to those obtained in the first analysis, in which the exclusion criteria were restricted to diagnosed infection, either active or within the previous two weeks (data not shown).

DISCUSSION

In this prospective study, high hsCRP levels were significantly associated with an increased risk of perioperative AMI.

In a recent prospective study of patients undergoing peripheral vascular surgery, Owens and colleagues[22] showed similar results, demonstrating that high hsCRP levels (>5 mg/L) were associated with cardiac events and graft complications.

It is important to differentiate this clinical context from hsCRP levels >1 mg/L, which are associated with low grade, chronic inflammation that represents a higher cardiac risk in long-term studies. Such levels are useful for evaluating cardiac risk in clinical practice (hsCRP levels from 1 to 3 and >3 mg/L represent medium and high risk, respectively). Concentrations >10 are usually considered indicative of acute inflammatory processes and should be confirmed with retesting after 2 weeks.[14] Ridker and colleagues, however, suggested, that extremely high hsCRP levels may be useful for predicting cardiovascular disease and thrombotic events,[25] as observed in the present study.

The high incidence of perioperative AMI and noncardiac deaths in our sample may be due to a combination of factors. Patients included in the sample had a >5% probability of AMI and cardiac deaths according to AHA/ACC 2002 criteria, which categorized them as high-risk surgery patients. Furthermore, their mean age was elevated (66 years), and they underwent urgent and even emergency procedures. With the significant evolution of endovascular and video-laparoscopic procedures, high-risk noncardiac surgery is currently performed only in the most severe cases with extensive disease and

Table 3 - Relative risk, absolute risk, sensitivity, specificity, and positive and negative predictive values for the cut-off point of ≥10 mg/L hsCRP.

	% events									
	<10 hsCRP	≥10 hsCRP	RR (95% CI)	AR (95%)	P	#ROC (95% CI)	S	Sp	+PV	-PV
AMI	0	13.9	-	13.9 (7.23-20.77)	0.005	0.85 (0.74-0.96)	100.0	67.7	13.9	100.0
Noncardiac death	9.2	0	-	-	0.096	0.32 (0.16-0.47)	-	62.1	-	90.8
Minor outcomes	33.8	47.2	1.4 (0.9-2.3)	13.4 (7.24-19.56)	0.206	0.61 (0.49-0.72)	43.6	69.4	47.2	66.2

AMI: acute myocardial infarction; hsCRP: high-sensitivity C-reactive protein in mg/L; RR: relative risk; PV: predictive value; AR: Absolute risk; ROC: area under the curve; S: sensitivity; Sp: specificity.

Table 4 - Odds ratio of major cardiac events in logistic regression analysis including hsCRP and CRI.

	OR	95% CI	p
hsCRP > 10	16.05	1.78 – 144.60	0.013
CRI ≥ 3	7.15	1.33 – 38.38	0.022

hsCRP: high-sensitivity C-reactive protein in mg/L; CRI: Cardiac Risk Index

comorbidities. A significant proportion of the patients in our sample presented invasive tumors and/or extensive vascular atherosclerosis. Approximately half of the patients presented two or more CRI predictors.[20]

In our sample, as previously reported in similar studies, CRI adequately classified the patients according to their risk of major cardiac complications. Perioperative AMI occurred in 25% of the patients with CRI ≥3 versus 1.2% of patients with CRI <2 (p = 0.002).

Perioperative AMI occurred during the first days after surgery, with four cases during the first 24 hours. None of the cases had ST-segment elevation, emphasizing the need to discuss routine postoperative care and screening. Because there is no routine analysis of biomarkers and/or cardiac enzymes in this type of surgery, two cases would have had delayed diagnoses. Two patients underwent percutaneous coronary intervention, one patient underwent CABG, and two patients received clinical treatment.

Some limitations of our study included the small absolute number of events and the relatively short follow-up, which included only the hospitalization period. However, because our main objective was to improve the in-hospital care of these patients, it is important to consider that our significant events were precisely those events that occur early in the intra- or postoperative period.

Our results suggest that there is a role for baseline hsCRP in predicting perioperative AMI in patients undergoing high-risk noncardiac surgery. Patients presenting with high hsCRP levels (>10 mg/L) could benefit from more rigorous preoperative assessment and careful postoperative follow-up. Interventions that reduce inflammation before surgery may also be helpful. Interestingly, recent studies have shown beneficial effects of statins in vascular surgery,[26,27] emphasizing this idea. Further studies are necessary to define the clinical impact and cost-effectiveness of including hsCRP levels in the scores for predicting cardiac risk during noncardiac surgery.

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