ESCVS article - Cardiac general

Preoperative B-type natriuretic peptide, and not the inflammation status, predicts an adverse outcome for patients undergoing heart surgery

Fernando Ganem*1, Carlos V. Serrano Jr1, Juliano L. Fernandes2, Maria Heloísa S.L. Blotta3,
Juliana A. Souza1, José C. Nicolau1, José A.F. Ramires3, Whady A. Hueb3

1Heart Institute (InCor), Medical School, University of São Paulo, São Paulo, Brazil
2Department of Clinical Pathology UNICAMP, Campinas, São Paulo, Brazil

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Abstract

Objectives: B-type natriuretic peptide (BNP) and inflammatory markers are implicated in the pathophysiology of both ischemic cardiomyopathy and complications after cardiac surgery with cardiopulmonary bypass (CPB). The purpose of this study was to assess preoperative and postoperative levels of BNP, interleukin-6 (IL-6), interleukin-8 (IL-8), P-selectin, intercellular adhesion molecule (ICAM), C-reactive protein (CRP) in patients undergoing cardiac surgery with CPB and investigate their variation and ability to correlate with immediate outcome. Methods: Plasma levels of these markers were measured preoperatively, 6 and 24 h after CPB in 62 patients. Main endpoints were requirements for intra-aortic balloon pump, intensive care unit (ICU) stay longer than five days, ventilator dependence >24 h, requirement for dobutamine, hospital stay >10 days, clinical complications (infection, myocardial infarction, renal failure, stroke and ventricular arrhythmias) and in-hospital mortality. Results: Preoperative BNP levels correlate with longer ICU stay (P<0.003), longer ventilator use (P=0.018) and duration of dobutamine use (P<0.001). The receiver-operating characteristic curve demonstrated BNP levels >190 pg/ml as predictor of ICU >5 days and BNP levels >20.5 pg/ml correlated with dobutamine use, with areas under the curve of 0.712 and 0.842, respectively. Preoperative levels of ICAM-1 were associated with in-hospital mortality (P=0.042). In the postoperative period, was found association between CRP, IL-6 and P-selectin with ventilation duration (P=0.013, P=0.006, P<0.001, respectively) and P-selectin with ICU stay (P=0.009). Conclusions: BNP correlates with clinical endpoints more than inflammatory markers and can be used as a predictor of early outcome after heart surgery.

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Keywords: Ischemic cardiomyopathy; Brain natriuretic peptide; Inflammation markers; Heart surgery

1. Introduction

Various clinical, laboratorial and hemodynamic factors have been tested with the intention to assess preoperative risk for patients with ischemic heart disease undergoing heart surgery [1, 2]. However, B-type natriuretic peptide (BNP) and inflammation determinations for the prognosis and management of heart surgery are still underestimated.

BNP is a neurohormone released in proportion to the increase in left ventricular (LV) wall tension caused by intraventricular pressure or stretch [3] and can be used as a reliable marker for diagnosis and prognosis in heart failure [4], aortic stenosis, myocardial infarction, pulmonary embolism [5] and sepsis [6].

Regarding inflammation, there is accumulating evidence that the inflammatory status plays an important role in the development of LV remodeling including structural and functional changes of the myocardium [7], heart failure, atherosclerosis and coronary disease [8].

Based on the hypothesis that patients with high BNP levels and/or a pro-inflammatory state before surgery would encounter increased events, we conducted this study in order to investigate the correlation between preoperative BNP levels and inflammation status and outcome of patients with coronary heart disease submitted to an elective heart surgery. Inflammation was denoted by interleukin (IL)-6, IL-8, soluble P-selectin, soluble intercellular adhesion molecule (sICAM)-1 and C-reactive protein (CRP). We also analyzed these markers in the postoperative period.

2. Material and methods

2.1. Study patients

We recruited prospectively 62 patients, referred to the Heart Institute (InCor HCFMUSP, São Paulo, Brazil) for open-
heart surgery, in compliance with the local Human Research Protection Program. All patients undergoing heart surgery at the Institute were eligible for inclusion, and every effort was made to recruit them in a consecutive order. The indication for coronary revascularization was independent of the study on the discretion of the attending physician based on the presence of ischemic and viable myocardium on provocative myocardial tests.

All patients were asymptomatic for heart failure, had hemodynamic stability and needed no oxygen support before surgery. The most relevant clinical and laboratory preoperative information is shown in Table 1.

Exclusion criteria were age above 75 years, concomitant inflammatory and consumptive diseases, acute infection, collagen disorders, renal failure (creatinine > 1.4 mg/dl), symptomatic heart failure [New York Heart Association (NYHA) class III–IV], respiratory distress, emergency surgeries, acute coronary syndromes, use of vasoactive drugs seven days before surgery date, coagulopathy, stroke and intensive care unit (ICU) patients.

Patient records were evaluated before knowledge of BNP and inflammation marker values. Past medical and surgical histories were determined by previous records. LV ejection fraction (LVEF) was evaluated by echocardiogram. Cardiac catheterization data was performed as indicated by the attending cardiologist, independent of the study. Clinical events were reported only after review and confirmation by an attending physician.

### 2.2. Clinical postoperative events

From the outcome data, clinical events were defined as:

- Requirement for intra-aortic balloon pump (IABP), ICU stay longer than five days, ventilator dependence > 24 h, requirement for dobutamine, hospital stay > 10 days, clinical complications (infection, myocardial infarction, renal failure, stroke and ventricular arrhythmias) and in-hospital mortality. We also analyzed the correlation of all markers with these events for all patients and separately for patients with preserved LVEF (> 0.40) and impaired LVEF (< 0.40).

### 2.3. Anesthetic and heart surgery procedure

All patients received similar standardized anesthetic and non-invasive and invasive monitoring techniques that are routinely performed at the Institute. Before connection of the circuit for cardiopulmonary bypass (CPB), heparin (300 IU/kg), metilprednisolone (1000 mg) and diphenidramine (50 mg) were administered to all patients. Standard surgical techniques were used under hypothermic arrest with blood cardioplegia, as described before [9]. All surgeries were performed on-pump.

### 2.4. Study protocol

Peripheral venous blood samples (10 ml) were obtained from patients preoperatively, 6 and 24 h after CPB. Samples were collected into a tube containing potassium ethylenediaminetetraacetic acid (EDTA), used as an anticoagulant. All serum samples for each individual were stored at −70 °C for subsequent enzyme-linked immunosorbent assays (ELISA).

BNP levels were determined using a fluorescence immunoassay kit (Biosite Diagnostics; San Diego, CA, USA). The precision and sensitivity of this kit has been previously described; normal values for BNP are < 100 pg/ml.

Commercial ELISA detecting cytokines IL-6 and IL-8 were applied. Measurements were performed in duplicate, at the same time by the same ELISA to avoid variation of assay conditions. Normal values for IL-6 were < 3.12 pg/ml and for IL-8, < 31.2 pg/ml.

For measuring the soluble adhesion molecules P-selectin and ICAM-1 concentrations, serum was separated by centrifugation of the blood samples from each patient and was stored at -70 °C. Commercial ELISA (R&D Systems; Minneapolis, MN, USA) were used. Plasma levels expected for healthy subjects of ELISA for sP-selectin and sICAM-1 were, respectively: 51 ng/ml to 113 ng/ml and 115 ng/ml to 306 ng/ml. The lower limits of detection for these inflammatory markers and the coefficient of variation for these measurements for sP-selectin and sICAM-1 were, respectively: 0.5 ng/ml and 15.6 pg/ml.

CRP was immediately measured with a high-sensitivity assay nephelometry (Dade Behring; Marburg, Germany) with an analytic sensitivity of 0.175 mg/l. The intra-assay variability for the lower assay range was < 0.165 mg/l. CRP levels above 1.0 mg/l were defined as increased.

### 2.5. Statistical analysis

The number of participants required to test our hypothesis was based on a prior study [10] reporting the relation between BNP increase and clinical events in a patient population. This study indicated that 37 patients undergoing coronary artery bypass grafting (CABG) were needed to detect a 20% increase in BNP, based on a power of 0.90 and an alpha error of 0.05.

Data are expressed as the mean values ± S.D. χ² analyses and Fisher’s exact tests were used for categorical variables. The correlation of each marker with clinical events was evaluated using Spearman test. Mann–Whitney test was used for a comparison of clinical variables between preserved and impaired LVEF patients. The utility of markers and ejection fraction in predicting postoperative complications was evaluated using receiver-operating characteristic (ROC) curves.

A P-value < 0.05 was considered statistically significant.
3. Results

3.1. Patient characteristics

Data from surgical procedures and postoperative outcome are shown in Table 2. Of 62 patients, 46 (74.2%) underwent isolated CABG, while 16 (25.8%) needed associated procedures. Mortality numbers were concentrated in this last group, characterized by refractory response to the clinical treatment of heart failure despite being asymptomatic at rest before surgery: six out of seven deaths occurred in this group (five in patients undergoing CABG and aneurysmectomy and one in a patient that underwent CABG, aneurysmectomy and mitral valve replacement).

On postoperative subgroup analysis, patients with LVEF <0.40 required more dobutamine use (P < 0.001), had longer ventilator dependence (P < 0.002) and longer ICU stay (P < 0.001) than patients with LVEF >0.40. However, regarding duration of dobutamine use, IABP requirement, creatine phosphokinase MB elevation, clinical complications (infection, myocardial infarction, renal failure, stroke and cardiac arrhythmias) and in-hospital mortality, no differences were noted.

3.2. Correlation between markers and clinical postoperative events

Statistical analysis with Mann–Whitney and Spearman test verified the correlation of each marker with clinical events and is briefly described as follows. The levels of each marker are shown in Table 3.

3.2.1. BNP

Preoperative BNP levels correlated with longer ICU stay (r = 0.381, P = 0.003), longer mechanical ventilation (r = 0.271, P = 0.018) and longer dobutamine use (r = 0.606, P < 0.001). BNP at 6 h post-CABG correlated with longer ICU stay (r = 0.274, P = 0.039), longer need of mechanical ventilation (r = 0.271, P = 0.041) and longer dobutamine use (r = 0.558, P < 0.001). BNP at 24 h post-CABG correlated with longer dobutamine use (r = 0.418, P = 0.003).

3.2.2. CRP

At 6 h after CABG, CRP correlated with longer ICU stay (r = 0.331, P = 0.013) and longer dobutamine use (r = 0.359, P = 0.007). Before and 24 h after surgery, CRP did not correlate with postoperative events.

3.2.3. IL-6

Preoperatively IL-6 correlated with longer dobutamine use (r = 0.308, P = 0.018). At 6 h after CABG IL-6 did not correlate with events. IL-6 at 24 h after CABG correlated with longer dobutamine use (r = 0.382, P = 0.006).

3.2.4. IL-8

Preoperative and 6 and 24 h postoperative levels of IL-8 did not correlate with postoperative events.

3.2.5. P-selectin

After 24 h of surgery, P-selectin correlated with longer mechanical ventilation (r = 0.436, P = 0.001) and longer ICU stay (r = 0.358, P = 0.009). Other levels of P-selectin had no correlations with events.

3.2.6. ICAM-1

Preoperative levels of ICAM-1 correlated with in-hospital mortality (r = 0.322, P = 0.042). ICAM-1 at 6 and 24 h after CABG had no correlation with events.

Table 3. Marker levels preoperatively, 6 h and 24 h postoperatively

<table>
<thead>
<tr>
<th>Marker</th>
<th>Preoperative</th>
<th>6 h</th>
<th>24 h</th>
<th>Preoperative-6 h</th>
<th>Preoperative-24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P-value</td>
<td>P-value</td>
<td>P-value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>9.22 ± 19.84</td>
<td>70.62 ± 74.71</td>
<td>38.06 ± 43.84</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-8 (pg/ml)</td>
<td>23.09 ± 71.23</td>
<td>34.57 ± 39.59</td>
<td>26.39 ± 28.49</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sICAM-1 (ng/ml)</td>
<td>134.25 ± 57.79</td>
<td>117.28 ± 48.27</td>
<td>126.91 ± 64.07</td>
<td>&lt;0.001</td>
<td>ns</td>
</tr>
<tr>
<td>sP-selectin (ng/ml)</td>
<td>81.29 ± 32.51</td>
<td>86.16 ± 35.59</td>
<td>70.21 ± 22.62</td>
<td>ns</td>
<td>0.033</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>6.56 ± 10.44</td>
<td>35.33 ± 43.63</td>
<td>99.65 ± 43.95</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>129.04 ± 179.33</td>
<td>182.71 ± 221.70</td>
<td>234.95 ± 263.83</td>
<td>ns</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Preoperative-6 h, variation before and 6 h after cardiopulmonary bypass; preoperative-24 h, variation before and 24 h after cardiopulmonary bypass. IL, interleukin; sICAM, soluble intercellular adhesion molecule; sP-selectin, soluble P-selectin; CRP, C-reactive protein; BNP, brain natriuretic peptide.
No correlations between markers and clinical events, such as IABP use, infection, myocardial infarction, renal failure, stroke and ventricular arrhythmias were found. Furthermore, none of the markers correlated with postoperative events, when analyzed in patients with preserved LVEF vs. impaired LVEF patients.

In addition, ROC curves were used to evaluate the ability of each marker to predict intra- and postoperative complications. Figs. 1 and 2 show ROC curves relating preoperative BNP levels to ICU > 5 days and need of dobutamine use, respectively. BNP levels > 190 pg/ml was a strong predictor of ICU stay > 5 days, with an area under the curve of 0.712 (sensitivity = 60%, specificity = 84.4%, accuracy = 82.5%, odds ratio = 8.2, positive predictive value = 25%, negative predictive value = 96.8%). ROC, receiver-operating characteristic; BNP, B-type natriuretic peptide.

3.3. Levels of BNP and inflammatory markers preoperatively

As a subanalysis we verified preoperative levels of markers considering LVEF. BNP and sICAM-1 levels were higher in patients with LVEF < 0.40 vs. LVEF > 0.40 (BNP = 207.5 ± 201.5 vs. 30.2 ± 67.1, P < 0.001) and (sICAM-1 = 146.6 ± 62.1 vs. 119.2 ± 48.8, P = 0.041). Regarding the other inflammatory markers, no significant differences were noted before heart surgery.

4. Discussion

An extensive number of investigations have been carried out in an attempt to elucidate postoperative morbidity and mortality in patients undergoing coronary revascularization. However, very few studies evaluated the behavior of these markers before and after CABG with CPB, their temporal curves and correlation with clinical events.

4.1. Inflammatory markers

The correlation of inflammatory markers to worse outcomes in cardiac surgeries has been a matter of controversy in the literature. Fransen et al. [11] found that higher CRP levels before surgery were associated with the development of postoperative infections. Biancari et al. [12] found correlations with low output syndrome, neurological events and mortality. However, in the present study as well as in Gaudino et al. [13] none of these correlations were observed. These differences might have occurred due to the population characteristics in each study specifically in the presence or not of patients with acute disease, which are known to show better correlation with these inflammatory markers.

Our study does not seem to support a strong role for the use of inflammatory markers in predicting events after cardiac surgery. Preoperatively, considering that all study patients had ischemic heart disease, with indication for coronary revascularization, a proinflammatory state would have been expected. This was in fact observed in this study, since patients presented higher levels of CRP and IL-6 than normal before surgery, suggesting a baseline inflammatory state, independent of LVEF function. However, correlations with events were relatively weak and only sICAM-1 corre-
lated with in-hospital mortality and IL-6 correlated with longer dobutamine use. No correlations between other preoperative inflammatory marker levels and outcome were detected. This lack of correlation suggests that the complexities of factors involved in cardiac artery disease as well as all variables involved in cardiac surgery might offset any minor effect that inflammation might play in this situation. Differently from acute clinical settings, where these substances have been shown to be not only markers but also active triggers of events involved in the molecular mechanisms of plaque destabilization [14], in the stable patient undergoing revascularization this role seems to be much more restricted.

In the postoperative period, patients presented an inflammatory response to open-heart surgery as expected characterized by an increase on IL-6, P-selectin and CRP. This finding is in accordance to other reports [15] that also detected evidences of inflammation after surgery mainly with CPB. Serrano et al. [16] verified a reduced expression of systemic proinflammatory and myocardial biomarkers after off-pump versus on-pump coronary artery bypass surgery. Other authors verified that conventional CABG with CPB and cardiac arrest is associated with postoperative infection and more intensive inflammatory response than CABG on the beating-heart [17]. However, these findings did not significantly correlate to postoperative events nor resulted in meaningful ROC curves that could be used to clinically guide the postoperative follow-up of these patients.

4.2. BNP

Several studies have been published expressing BNP as an important predictor for patients with heart failure under clinical treatment [18]. However, only a few studies verified preoperative BNP as a predictor for outcome in cardiac surgery. Also, recent evidence [19, 20] revealed BNP's ability in predicting postoperative events in patients undergoing major non-cardiac surgery – independent of other risk factors.

Our study found that preoperative BNP levels correlated with longer ICU stay, longer mechanical ventilation and longer dobutamine use. BNP at 6 h post-CABG correlated with longer ICU stay, longer need of mechanical ventilation and longer dobutamine use. BNP at 24 h post-CABG correlated with longer dobutamine use. Other authors found association between BNP concentration and outcome. Hutfless et al. [21] observed that preoperative BNP is associated with longer in-hospital stay, IABP requirement and one-year mortality, independently of LVEF. Attaran et al. [22] verified that postoperatively, high BNP concentration predicted inotropic use, longer ventilation time, longer hospital stay and early mortality for patients undergoing cardiac surgery. Other investigators [23] observed that preoperative BNP levels are predictive for the development of atrial fibrillation.

More recently, Eliasdottir et al. [24] observed in patients undergoing various cardiac procedures that preoperative N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels were higher among patients with an ICU length of stay of more than two days, and those who needed inotropic agents, IABP insertion and developed renal failure. Jogia et al. [25] also observed that preoperative NT-pro-BNP are associated with a slow postoperative recovery, but do not predict mortality or atrial fibrillation.

The present study confers preoperative BNP cut-off levels >190 pg/ml the power to predict longer ICU stay among stable patients undergoing heart surgery. Interestingly, differently than anticipated, preoperative LVEF did not demonstrate any significant ROC curves when compared with the clinical events, a finding also observed by Hutfless et al. [21].

4.3. Clinical implications

We judge that this investigation revealed two apparently new findings that are relevant for clinical practice. First, that preoperative BNP is a strong predictor of an adverse postoperative outcome as reflected by longer ICU stay and need for dobutamine use for asymptomatic and stable coronary artery disease patients, regardless of LV function. Second and in the opposite direction, preoperative inflammation, represented by the markers studied (which included CRP), had a poor correlation with complications after surgery, independently of LVEF. Notably, the ability of BNP to predict postoperative complications was more accurate than levels of inflammatory markers. To our knowledge, no other investigation evaluated simultaneously the prognostic impact of both BNP and inflammatory markers in this setting.

4.4. Limitations

The authors recognize that this study is not the first to investigate BNP utility as a prognostic tool in cardiac surgery, has a small sample, was performed in a single centre and consequently does not allow strong conclusions. While we are not able to offer a cut-off value for complications, preoperative BNP >190 pg/ml correlated with longer ICU stay with a considerable accuracy. The limited numbers prevented us from analyzing the data in a multivariate way, specifically with the inclusion of CPB and cross-clamp times. Finally, the use of methylprednisolone before CPB might have reduced the inflammatory response observed postoperatively and interfered with this evaluation. However, the use of corticosteroids in this situation is already routine and we thought it would be unethical to withhold its use in this setting despite the risk of jeopardizing the data.

In conclusion, the authors believe that BNP, associated with other clinical and laboratorial characteristics, should be used routinely, in order to identify patients at risk for longer ICU stay. Importantly, preoperative inflammation markers and LVEF by echocardiogram did not satisfactorily predict outcomes after cardiac surgery. Finally, BNP utility is independent of other conventional indicators of risk.

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References


