High concentrations of N-BNP are related to non-infectious severe SIRS associated with cardiovascular dysfunction occurring after off-pump coronary artery surgery†

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Background. Procalcitonin (PCT) blood concentrations are known to be an appropriate marker of severe systemic inflammatory response syndrome (SIRS) induced by coronary artery surgery with and without cardiopulmonary bypass. Pro-brain natriuretic peptide (N-BNP) is a newly described cardiac hormone considered to be an effective marker of severity and prognosis of acute coronary syndromes and congestive heart failure. We evaluated the perioperative time courses of PCT and N-BNP and investigated their role as early markers of severe SIRS (SIRS with cardiovascular dysfunction) induced by off-pump coronary artery bypass (OPCAB).

Methods. Sixty-three patients were prospectively included. The American College of Chest Physicians Classification was used to diagnose SIRS and organ system failure to define severe SIRS. Serum concentrations of PCT and N-BNP were determined before, during and after surgery. Receiver operating characteristic curves and cut-off values were used to assess the ability of these markers to predict postoperative severe SIRS.

Results. SIRS occurred in 25 (39%) patients. Nine of them (14%) showed severe SIRS. Significantly higher serum concentrations of N-BNP and PCT were found in patients with severe SIRS with peak concentrations respectively at 8887 pg ml\(^{-1}\) (range 2940–29372 pg ml\(^{-1}\)) for N-BNP and 9.50 ng ml\(^{-1}\) (range 1–65 ng ml\(^{-1}\)) for PCT. The area under the curve using N-BNP to detect postoperative severe SIRS was 0.799 before surgery (0.408 for PCT; \(P<0.01\)) and 0.824 at the end of surgery (0.762 for PCT; \(P<0.05\)).

Conclusions. N-BNP may be an appropriate marker indicating the early development of non-infectious postoperative severe SIRS after OPCAB.

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Systemic inflammatory response syndrome (SIRS) describes the clinical symptoms observed after various infectious and non-infectious insults. This generalized inflammatory response is common after coronary artery bypass grafting (CABG) with or without cardiopulmonary bypass (CPB). Factors such as surgical trauma, myocardial ischaemia–reperfusion, body temperature and cytokine cascade have been also shown to induce SIRS after coronary artery surgery with or without CPB. This inflammatory cascade may result, in some patients, in severe postoperative complications including renal, hepatic and neurological dysfunction, or respiratory and cardiovascular failure, thus prolonging intensive care unit (ICU) stay. Patients with SIRS associated with organ dysfunction can be classified as having severe SIRS, a definition which has been used after coronary artery surgery.  

†This article is accompanied by Editorial II.
Procalcitonin (PCT) is a propeptide of calcitonin produced by the thyroid gland. Usually undetectable in healthy subjects, attention has recently been drawn to it as a possible marker of the systemic inflammatory response.

Pro-brain natriuretic peptide (N-BNP) is a newly described cardiac hormone secreted by the ventricles. It has recently been considered as an effective marker of severity and prognosis of acute coronary syndromes and congestive heart failure. However, data comparing induction of BNP and PCT after surgery, especially with cardiovascular complications, are not available.

The aim of this prospective study was to investigate the relationships between N-BNP and PCT plasma concentrations in patients with uncomplicated (no SIRS) and complicated postoperative courses (severe SIRS) after CABG using the off-pump technique. The relationship between PCT, N-BNP and complication risk was assessed using receiver operating characteristic (ROC) curves.

**Material and methods**

**Patient selection**

After approval from the university ethics committee and written informed consent, 67 consecutive eligible patients undergoing elective off-pump coronary artery bypass grafting (OPCAB) were enrolled prospectively between December 2001 and December 2002. Sixty-three of them were free from active preoperative infection or inflammatory disease. Their preoperative medication did not include any antibiotic or corticosteroid. Four patients were withdrawn from the study because of preoperative infection such as urinary infection or acute bronchitis. Preoperative left ventricular ejection fraction was lower than 0.4. Antibiotic prophylaxis was i.v. cefamandole 1.5 g after induction and 750 mg every 2 h during the whole surgery period.

During surgery, temperature was maintained with a warming blanket. A cell saver was used to minimize homologous blood transfusion.

Heparin dosage was 150 IU kg$^{-1}$ to reach ACT$>300$ s. Surgical technique was standardized, and all procedures were performed by the same surgeon. The left internal mammary artery was attached to the left anterior descending artery, and vein grafts to other coronary arteries as appropriate in all patients. The top end anastomoses were constructed with the help of a side-biting clamp. Coronary artery immobilization was achieved with a mechanical stabilizer (Octopus 3; Medtronic, Minneapolis, MN, USA). At the end of surgery, i.v. protamine sulphate was administered to obtain ACT$<160$ s.

**Postoperative management**

Tracheal extubation was performed when patients met the full criteria described in a previous study. Starting on postoperative day 1, patients received aspirin 250 mg i.v. daily during mechanical ventilation and 160 mg orally daily after extubation. The patients were discharged from the ICU usually on the second postoperative day and the postoperative course monitored until the seventh postoperative day.

**Blood samples**

Blood samples were collected 30 min after induction of i.v. anaesthesia, before surgery (T0), 10 min (T1) and 4 h (T2) after the end of the surgery and on the first (T3), second (T4) and third (T5) days after surgery at 5 a.m. Blood samples were collected from the cannulated radial artery and immediately centrifuged for 20 min. Plasma samples frozen at $-80^\circ$C were stable for assays for >20 days after sampling, and all samples were analysed within 2 weeks.

**N-BNP and PCT determinations**

N-BNP concentrations were measured with a sandwich immunoassay using polyclonal antibodies that recognize epitopes located in the N-terminal part (1–76) of proBNP (1–108). An electrochemiluminescence immunoassay was performed using an Elecsys analyser (Roche Diagnostics, Mannheim, Germany). The intra-assay coefficients of variation were 2.7% (at 175 pg ml$^{-1}$) and 1.9% (at 1068 pg ml$^{-1}$), respectively, and the interassay coefficients of variation were 3.2% (at 175 pg ml$^{-1}$) and 2.6% (at 1068 pg ml$^{-1}$).

The PCT concentrations in serum were measured by immunoluminometric assay with the commercially available LUMI test PCT (Brahms Diagnostica, Berlin, Germany). The inter-assay precision of the kit was 6–10%; the lower limit detection was 0.1 ng ml$^{-1}$. 
Definitions of SIRS and severe SIRS

After surgery, microbiological and radiological examinations were performed daily until ICU discharge. SIRS was defined according to the classification of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference.\(^{15}\) Severe SIRS was defined as SIRS with one or more postoperative organ dysfunction. The criteria for defining these organ dysfunctions were obtained from the ODIN model to characterize and predict the outcome of ICU patients.\(^{6}\) SIRS classification was performed on all patients on the first postoperative day at 5 a.m. and daily on patients who remained longer in the ICU. Cardiac operative risk was evaluated using the EuroSCORE and Parsonnet Index scoring systems, on the first postoperative day, by the same investigator, who was blinded to the PCT and N-BNP values.\(^{16,17}\)

Infection status

Before and after operation, clinical assessment, including body temperature and radiological examination, were performed daily until ICU discharge. Microbiological examination of sputum, blood and urine was requested when infection, bacteraemia or sepsis was suspected.

Statistical analysis

Associations between SIRS and predictive or prognostic factors were analysed using the \(\chi^2\) test or Fisher’s exact test when appropriate for discrete variables or using the Mann–Whitney \(U\)-test for continuous variables.

The variation over time (T0–5) of N-BNP and PCT was analysed according to SIRS status using analysis of variance for repeated measurements with SIRS as explicative factor. Values were expressed as mean (SD).

Receiver operating characteristic (ROC) curves were used to evaluate N-BNP and PCT data in relation to SIRS. The ROC curve is a graphic means of assessing the ability of a screening test to discriminate between two states. The area under the curve is a quantitative index describing a ROC curve. Values higher than 0.6 or 0.7 were considered to be informative. Cut-off values, defined as the threshold values that maximized the sum of sensitivity and specificity, were determined for each score with ROC curves. Areas under the curve were calculated and compared using the Hanley–McNeil non-parametric method.\(^{18}\)

For all tests, \(P\)-values < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS software, version 11.1 for Windows.

Results

Sixty-three patients were included in the study. Simple SIRS developed in 16 patients (25\%) and severe SIRS in nine patients (14\%). All presented with postoperative cardiovascular dysfunction. Mean age, body weight, NYHA status and preoperative creatinine clearance were not significantly different between groups. Preoperative LVEF was significantly lower in the severe SIRS group compared with the others (46 (9)\% for severe SIRS, 59 (12)\% for SIRS and 58 (7)\% for patients without SIRS, \(P<0.03\)). Parsonnet score and EuroSCORE were not significantly different between groups. There was no difference in the number of grafts between groups.

Duration of tracheal intubation was significantly longer in patients with severe SIRS compared with those without organ dysfunction or without SIRS (78.2 (28.2) h, 7.3 (4.5) h and 6.5 (4.8) h, respectively, \(P<0.01\)). Duration of stay in the ICU was significantly prolonged in patients with severe SIRS (10.8 (11), 3.2 (1.1) and 2.3 (0.6) days, \(P<0.01\)).

Peroperative haemodynamic values and measurements of body temperature did not show any statistically significant difference between patients with or without SIRS. Requirement for postoperative inotropic support was significantly greater in patients with severe SIRS. Severe SIRS was associated with highest doses of dobutamine (8 (2) \(\mu\)g kg\(^{-1}\) min\(^{-1}\)) and epinephrine (0.26 (0.16) \(\mu\)g kg\(^{-1}\) min\(^{-1}\)) when compared with patients with simple SIRS (2.1 (1.1) and 0.05 (0.03) \(\mu\)g kg\(^{-1}\) min\(^{-1}\), \(P<0.05\)) or without SIRS (0.6 (1.2) and 0.0 (0.0) \(\mu\)g kg\(^{-1}\) min\(^{-1}\), \(P<0.05\)). Epinephrine and dobutamine were required in seven patients with severe SIRS (77\%) to maintain systolic arterial pressure >90 mm Hg. One patient required placement of an intra-aortic balloon pump counterpulsation for refractory low cardiac output. Two of the 63 patients required norepinephrine.

Plasma N-BNP concentrations in the group without SIRS were normal before and after surgery, peaked 48 h after surgery (T4) (798 (588) pg ml\(^{-1}\); range 437–2600 pg ml\(^{-1}\)), and began to decrease at 72 h (T5). The time course of N-BNP was not significantly different between Groups 1 (no SIRS) and 2 (simple SIRS) (Fig. 1). In patients with severe SIRS, plasma N-BNP concentrations were significantly higher than in the two other groups at each time point (\(P<0.001\)) and were abnormal before surgery (2561 (4190) pg ml\(^{-1}\); range 284–15021 pg ml\(^{-1}\)), after surgery (2583 (3625) pg ml\(^{-1}\); range 298–12778 pg ml\(^{-1}\)), and peaked at 72 h after surgery (T5) (8887 (7196) pg ml\(^{-1}\); range 2940–29372 pg ml\(^{-1}\)).

In all patients, intraoperative measurements of serum PCT (T0, T1) resulted in values of less than 0.97 ng ml\(^{-1}\) (not significant) and a peak concentration was reached on the second postoperative day (Fig. 2). The rise in PCT concentration was significantly greater in patients with severe SIRS than in the other patients from the fourth hour after surgery up to the third postoperative day. No significant difference was detected between patients with simple SIRS and those without SIRS.

ROC analysis was used to calculate sensitivity and specificity for cardiovascular complications associated with SIRS at different concentrations of PCT and N-BNP (Figs 3–5). The areas under the curves (AUCs) for N-BNP...
were, respectively, 0.799 (P=0.002; 95% CI 0.626–0.972) at T0, 0.824 (P=0.001; 95% CI 0.654–0.993) at T1 and 0.912 (P=0.001; 95% CI 0.823–1) at T2. The AUCs for PCT were 0.408 (P=0.348; 95% CI 0.212–0.604) at T0, 0.762 (P=0.007; 95% CI 0.599–0.930) at T1 and 0.766 (P=0.007; 95% CI 0.599–0.933) at T2.
operative cardiovascular morbidity. Benefit of off-pump coronary artery bypass in terms of post-study by Demaria and colleagues, who did not show any calcitonaemia was related to non-infectious postoperative morbidity. Circulation may cause SIRS, which may be complicated with SIRS.

N-BNP concentrations appearing to be a better predictor than PCT for postoperative cardiovascular events associated with severe SIRS. We found that postoperative severe SIRS was associated with significantly higher serum N-BNP and PCT concentrations, found that postoperative severe SIRS was associated with cardiovascular dysfunction after off-pump coronary artery surgery. We demonstrated that postoperative severe SIRS associated with cardiovascular dysfunction was associated with lower preoperative LVEF. This complements the published evidence linking N-BNP concentrations to haemodynamic and echographic state in heart diseases.

Fig 5 Receiver operating characteristic (ROC) analysis of NT-pro-brain natriuretic peptide (N-BNP) and procalcitonin (PCT) for the diagnosis of SIRS with postoperative cardiovascular complications at T2 (4 h after surgery).

Discussion

This study was the first designed to examine the role of N-BNP and procalcitonin as early markers of severe systemic inflammatory response associated with cardiovascular dysfunction after off-pump coronary artery surgery. We found that postoperative severe SIRS was associated with significantly higher serum N-BNP and PCT concentrations, N-BNP concentrations appearing to be a better predictor than PCT for postoperative cardiovascular events associated with SIRS.

Cardiovascular surgery with or without extracorporeal circulation may cause SIRS, which may be complicated by the development of organ system dysfunction, including acute lung injury, shock and renal failure (severe SIRS). Using the definitions given by the Consensus Conference of the American College of Chest Physicians/Society of Critical Care Medicine, we found that SIRS occurred in 39% of our patients. The incidence of SIRS is lower than that reported in previous studies after cardiac surgery with cardiopulmonary bypass, but the incidence of severe SIRS is similar. This finding is in agreement with a previous study by Demaria and colleagues, who did not show any benefit of off-pump coronary artery bypass in terms of postoperative cardiovascular morbidity.

PCT has been suggested as a specific marker of the severity of sepsis and infection. High serum concentrations of PCT have been found in SIRS associated with severe burns or after trauma. Hyperprocalcitonaemia has been associated with the early development of pulmonary or cardiovascular complications after cardiopulmonary bypass. In a recent study, we have shown that hyperprocalcitonaemia was related to non-infectious postoperative severe SIRS associated with cardiovascular dysfunction after coronary artery bypass graft surgery.

N-BNP has been proposed recently as an effective marker of the severity and prognosis of acute coronary syndromes and congestive heart failure.

It is of interest to investigate the role of PCT and N-BNP as markers of severe SIRS after off-pump coronary artery surgery. Our data confirm that plasma N-BNP concentrations are raised in cardiac disease in proportion to the severity of left ventricular dysfunction and that the preoperative plasma concentrations of N-BNP could be a valuable predictor of severe SIRS associated with cardiovascular dysfunction. In a previous study of patients after CABG with CPB, we demonstrated that postoperative severe SIRS associated with cardiovascular dysfunction was associated with lowest preoperative LVEF. This complements the published evidence linking N-BNP concentrations to haemodynamic and echographic state in heart diseases. A preoperative N-BNP >500 pg ml$^{-1}$ appears to indicate a greater risk of postoperative cardiovascular complications associated with SIRS, as above this threshold the sensitivity was 75% for patients developing postoperative complications and SIRS. The AUC of the ROC analysis for cardiovascular complications was 0.799, significantly different from the AUC for PCT (0.408).

The mechanism of production of BNP is unclear. Low preoperative LVEF, associated with subacute preoperative myocardial ischaemia, may increase regional ventricular wall stretch owing to local depression of myocardial contraction. Mechanical stretch could therefore stimulate N-BNP secretion and augment the messenger RNA expression of IL-6 and cardiotrophin I, a cytokine of the IL-6 family. However, IL-6 concentrations are also raised in cardiac surgery without CPB, and could be involved in the cytokine cascade after surgery.

The normal range of serum PCT concentration after cardiac surgery without CPB has not been clearly defined. Aouifi and colleagues showed that PCT concentrations increased after surgery, irrespective of the type of cardiac surgery, with a peak on the first postoperative day. In our study, postoperative changes in PCT concentrations were delayed. Over the 3 days after surgery, PCT concentrations remained <0.61 ng ml$^{-1}$ in patients without any complications, including patients with SIRS but without any organ dysfunction. These results are close to those reported by Kilger and colleagues (0.7 ng ml$^{-1}$), who clearly demonstrated that procalcitonin was a marker of systemic inflammatory response after conventional or minimally invasive CABG. All patients who developed organ dysfunction had a significantly increased PCT concentration from 4 h after surgery, which peaked on the second postoperative day. In most patients, this PCT elevation was noted before detection of any organ dysfunction. In our study, postoperative PCT concentrations >1.4 ng ml$^{-1}$ were related to postoperative severe SIRS.
Study limitations
We did not evaluate the role of N-BNP and PCT in predicting long-term prognosis. The population studied was homogeneous, but the limited number of patients associated with different postoperative cardiovascular complications did not allow us to determine a predictive value for each type of cardiovascular complication.

Our data do not provide information about the source of PCT and N-BNP production. The association with low preoperative LVEF may provide specific conditions leading to high early N-BNP and PCT concentrations.

In summary, markedly increased plasma concentrations of N-BNP and PCT were associated with postoperative SIRS and cardiovascular dysfunction. Preoperative N-BNP concentration appeared to be a better predictor and may be an appropriate early indicator of non-infectious postoperative cardiovascular complications. Further studies are needed to clarify the relationship between cytokine production and N-BNP release in severe SIRS after coronary artery surgery without CPB.

References