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Perioperative Indicators of Stress Response and Postoperative Inflammatory Complications in Patients Undergoing Off-Pump Coronary Artery Bypass Surgery

— A Prospective Observational Study —

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Background Little has been published regarding the association between perioperative stress response and clinical outcomes after off-pump coronary artery bypass surgery (OPCAB). The role of perioperative stress response in postoperative inflammatory complications (PIC) in patients undergoing OPCAB was assessed.

Methods and Results The study cohort consisted of 100 patients who underwent elective OPCAB over a 5-month period. Anesthetic management was standardized and blood samples were collected before surgery, immediately after surgery, and 1, 2, 3, and 7 days after surgery. Leukocyte, neutrophil, platelet, erythrocyte sedimentation rate, C-reactive protein, fibrinogen, cortisol, D-dimer, and fibrin degradation product were measured at each time point, and the association of each parameter with PIC was assessed. PIC included postoperative pulmonary complications, atrial fibrillation, and wound infections. PIC occurred in 30 patients at the median third postoperative day. Multivariate analysis showed preoperative cortisol (p=0.024) and cortisol on the first postoperative day (p=0.001) were significantly associated with PIC. Intraoperative cortisol release was correlated with intraoperative hemodynamic changes, including pulmonary artery pressure, central venous pressure, and cardiac index.

Conclusions Patients with PIC after OPCAB have significantly increased preoperative cortisol and cortisol on the first postoperative day. Intraoperative cortisol release was significantly correlated with hemodynamic changes. The neurohormonal environment and inflammatory response during and after beating-heart surgery should be further explored. (*Circ J* 2008; **72:** 1966 – 1974)

Key Words: Cortisol; Off-pump coronary artery bypass surgery

Patients undergoing cardiac surgery under cardiopulmonary bypass (CPB) frequently experience systemic inflammatory reactions that could result in increased postoperative morbidity and prolonged hospital stay[1] Important features of these inflammatory reactions include the activation of complement[2] and leukocytes[1] the release of proinflammatory cytokines[3] alterations in nitric oxide metabolism[4] and increased production of oxygen free radicals, which in some cases leads to oxidant stress injury[5,6] Among the strategies used to reduce the inflammatory reactions induced by CPB and its consequences are treatment with steroids[7] aprotinin[8,9] heparin-coated CPB circuits[10] and hemofiltration[11]

The omission of CPB itself might be a more radical and effective way of counteracting the effects of these inflammatory reactions and oxidative stress. For example, the rate of postoperative morbidity is reduced in patients undergoing cardiac operations without CPB[12] and inflammatory reactions in patients undergoing bypass graft operations were reduced when CPB was not used[13,14] Although avoidance of CPB should provide a more physiological milieu and reduce the perioperative stress response, with preservation of perioperative organ function, little has been published regarding the association of perioperative stress response and clinical outcomes after off-pump coronary artery bypass surgery (OPCAB). We therefore assessed the role of perioperative systemic inflammation and stress response on postoperative inflammatory complications (PIC) in patients undergoing OPCAB.

Methods

The patient cohort consisted of all patients scheduled for isolated primary OPCAB between May and September 2007. Patients undergoing emergency surgery and those with a history of previous cardiac surgery, preoperative exposure to warfarin sodium, platelet glycoprotein IIb/IIIa inhibitors, or thrombolytics were excluded. The 100 included patients were divided into 2 groups: the PIC group (n=30, 30%), consisting of patients with evidence of PIC; and the non-PIC group (n=70), consisting of patients with no evidence of PIC.

The study protocol was approved by our institutional re-

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view board (Yonsei IRB No. 4-2007-0135), and written informed consent was obtained from each patient.

Definitions of PIC

PIC included the following 3 conditions: postoperative pulmonary complications; postoperative atrial fibrillation; and wound infections.

Postoperative Pulmonary Complications

Acute respiratory distress syndrome was defined as: (1) acute onset with a PaO_2/fraction of inspired oxygen of 200 mmHg or less. (2) Bilateral infiltrates: the infiltrates might be patchy, diffuse, homogeneous, or asymmetrical, and should be consistent with pulmonary edema or fibrotic changes associated with fibroproliferation. Opacity as a result of pleural effusions or atelectasis should not be considered. Unilateral infiltrate was included for pneumonectomy patients. (3) No evidence of left atrial hypertension. If measured, a pulmonary artery wedge pressure must be 18 mmHg or less. (4) The 3 previously cited criteria must occur together within a 24-h interval![15,16]

Acute lung injury was defined as: (1) acute onset with a PaO_2/fraction of inspired oxygen of 300 mmHg or less; (2) bilateral infiltrates; and (3) no evidence of left atrial hypertension. If measured, a pulmonary artery wedge pressure of 18 mmHg or less.

For pulmonary infection, (1) pneumonia was diagnosed on the basis of a compatible chest radiograph and purulent sputum with Gram's stain and sputum culture documenting the presence of microorganisms; (2) aspiration pneumonitis was defined as either the presence of bilious secretion or particulate matter in the tracheobronchial tree, or, in patients who did not have their tracheobronchial airways directly examined after regurgitation, a postoperative chest radiograph with infiltrates not identified on a preoperative radiograph; sputum retention was defined as inability to adequately clear the tracheobroncheal secretions with standard physiotherapy, which was coincided with lobar or whole-lung atelectasis based on chest radiography requiring aspiration bronchoscopy. The diagnosis was essentially clinical, characterized by evidence of respiratory distress with rapid, shallow, and bubbly respirations. Bronchospasm was defined as a condition of respiratory dysfunction characterized by evidence of severe wheezing or a prolonged expiratory phase requiring aminophylline loading, aerosolized bronchodilator, β agonist, and steroid therapy.

Prolonged chest tube drainage was defined as drainage of pleural fluid equal or more than 2 weeks.

Postoperative Atrial Fibrillation

Postoperative atrial fibrillation was defined as an irregularly irregular supraventricular rhythm present in the absence of P waves that required treatment and that was typically sustained for more than 15 min. Arrhythmia data were collected and recorded for the first 7 postoperative days. Patients were continuously monitored in the cardiac surgery intensive care unit (ICU) with arterial, central venous, and pulmonary artery pressure monitoring and thermodilution cardiac output determination. Cardiac rhythm was continuously monitored in the ICU with bedside monitors and daily monitored with 12-lead electrocardiogram on the general ward until discharge.

Wound Infections

Wound infections were categorized into 3 types: impaired wound healing, superficial wound infections, and deep wound infections. Impaired wound healing was defined as wound erythema and a purulent discharge necessitating additional antibiotic agents and/or hospitalization. Diagnoses of superficial and deep infections were based on the wound swab culture results. The time interval for assessment of wound infection was the in-hospital period.

Anesthesia

All patients were managed according to the same anesthetic management protocol. Upon arrival in the operating room, each patient was linked to standard monitoring devices, including a pulmonary arterial catheter (Swan-Ganz CCOmbo CCO/SvO_2; Edwards Lifesciences, Irvine, CA, USA), before induction of anesthesia. After induction of anesthesia, a transesophageal echocardiography probe was inserted to detect newly developing segmental wall motion abnormalities. Intravascular volume replacement was managed with crystalloid and colloid solutions to maintain the pulmonary capillary wedge pressure between 8 and 16 mmHg, depending on baseline values. Central temperature, as measured by pulmonary arterial catheter, was maintained between 36°C and 37°C with a warm mattress, forced warm air blanket, and fluid warmer, as necessary.

Surgical Procedure

All surgical procedures were performed by 1 surgeon (K.J.Y) through a median sternotomy, and the heart was displaced with a posterior pericardial stitch and tissue stabilizer. The grafting sequence consisted of the left anterior descending coronary artery first, followed by the left circumflex coronary artery and the right coronary artery. During the period of heart displacement, mean systemic arterial pressure was maintained above 60 to 70 mmHg with a 10° to 20° Trendelenburg position and/or norepinephrine infusion. Cell salvage was always used during surgery, and salvaged blood was reinfused before the end of the operation. Allogenic packed red blood cells were transfused when hemoglobin concentration fell below 8 mg/dl. After surgery, all patients were transferred to the ICU.

Intraoperative Hemodynamic Changes

Hemodynamic variables, including heart rate, mean arterial pressure, central venous pressure, mean pulmonary arterial pressure, cardiac index, and mixed venous oxygen saturation, were recorded 15 min after induction of anesthesia (baseline), 10 min after stabilizer application for left circumflex coronary artery grafting, and 15 min after sternum closure. The volume of infused fluids and urine output during surgery and for 12 h in the ICU were recorded, as was the amount of norepinephrine infused during the operation.

Blood Sampling

Arterial blood samples were collected before induction of anesthesia, at the end of surgery, and 1, 2, 3, and 7 days after surgery. Blood samples were collected into sterile tubes containing trisodium citrate anticoagulant or potassium EDTA.

Assessment of Inflammatory Reactions

Inflammatory response was assessed by measuring blood leukocyte and neutrophil count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fibrinogen, and cortisol. Fibrinogen concentrations were determined using the thrombin clotting method, with a normal range of 200 to 400 mg/dl.

Table 1 Preoperative Patient Characteristics

	PIC group (n=30) No. (%)	Non-PIC group (n=70) No. (%)	p value
Age (years)	66.8±7.2	62.4±10.5	0.038
Female	10 (33.3)	20 (28.6)	0.812
BMI (kg/m^2)	24.4±3.5	24.1±2.8	0.804
Obesity	13 (43.3)	25 (35.7)	0.506
Diabetes	11 (36.7)	24 (34.3)	1.000
IDDM	1 (3.3)	4 (5.7)	
NIDDM	10 (33.3)	19 (27.1)	
Hypertension	21 (70.0)	48 (68.6)	1.000
Dyslipidemia	13 (43.3)	34 (48.6)	0.667
s/p PTCA c stent	7 (23.3)	6 (8.6)	0.056
ARF	1 (3.3)	0 (0)	0.300
CRF	0 (0)	7 (10.0)	0.099
ESRD on dialysis	0 (0)	3 (4.3)	0.552
Renal transplantation	0 (0)	2 (2.9)	0.576
PAOD	3 (10.0)	16 (22.9)	0.170
Carotid stenosis	3 (10.0)	3 (4.3)	0.361
CVA	4 (13.3)	4 (5.7)	0.236
Smoking	14 (46.7)	33 (47.1)	1.000
Unstable angina	8 (27.6)	21 (32.3)	0.810
AMI	6 (20.0)	6 (8.6)	0.245
Arrhythmia	2 (6.7)	5 (7.1)	0.839
3-vessel disease	27 (90.0)	53 (76.8)	0.168
Left main disease	5 (16.7)	17 (24.3)	0.445
EF (%)	58.9±11.1	54.5±13.5	0.136
NYHA class			0.544
1	1 (3.3)	6 (8.6)	
2	14 (46.7)	36 (51.4)	
3	10 (33.3)	22 (31.4)	
4	5 (16.7)	6 (8.6)	
Standard Euroscore	3.7±3.6	2.7±1.9	0.156
Logistic Euroscore	5.6±12.2	2.5±2.0	0.187

PIC, postoperative inflammatory complications; BMI, body mass index; IDDM, insulin dependent diabetes mellitus; NIDDM, non-IDDM; PTCA c stent, percutaneous transluminal catheter angioplasty with stent insertion; ARF, acute renal failure; CRF, chronic renal failure; ESRD, end-stage renal disease; PAOD, peripheral artery obstructive disease; CVA, cerebrovascular accident; AMI, acute myocardial infarction; EF, ejection fraction; NYHA, New York Heart Association.

Serum cortisol concentrations were measured on a Bayer ACS-180 SE (Tarrytown, NY, USA) automated immunoassay analyzer using a competitive chemiluminescent assay (reference range from 07.00 to 09.00 h, 4.3–22.4 μg/dl). In this assay, cortisol in the sample competes with acridinium ester-labeled cortisol for binding to a polyclonal rabbit anti-cortisol antibody complex coupled to a solid phase. After a 5-min incubation, the solid phase is separated magnetically, and chemiluminescence is generated by the addition of hydrogen peroxide in an alkaline environment. The cortisol concentration is inversely proportional to the light emitted and is interpolated from a stored master curve.

Assessment of the Coagulation System

Platelet count, prothrombin time, activated partial thrombin time, and plasma concentrations of D-dimer and fibrin degradation product were measured serially over time.

Clinical Outcomes

The duration of mechanical ventilatory support, length of ICU stay, postoperative blood loss, transfusion requirements, and length of hospitalization were recorded. We defined PIC as postoperative pulmonary complications, postoperative atrial fibrillation, and wound infections. Patients were discharged from hospital when they were apyrexial, in an overall satisfactory stable condition, and able to perform basic routine tasks.

Postoperative Care

All patients were managed in the ICU for 2 nights. Unless otherwise indicated, all patients underwent extubation on the following morning. Intravenous patient-controlled analgesia was administered for several postoperative days, followed by pain control with oral analgesics. Emphasis was placed on aggressive pulmonary care, early ambulation, and pain control to minimize postoperative pulmonary complications.

Statistical Analysis

All data are presented as mean ± standard error of the mean. All statistical analyses were performed using the Statistical Package for Social Sciences Software version 12.0 (SPSS Inc, Chicago, IL, USA). Analysis of variance for repeated measurements was used to compare changes in time between the 2 patient groups. The significance levels of changes within groups were determined by the Mann–Whitney test. Survival curves were calculated by the Kaplan-Meier method and compared using the log-rank test. In all calculations, a p-value less than 0.05 was considered statistically significant.

Results

Study Population

The study population consisted of 100 patients (70 men and 30 women; mean age, 64.3±8.2 years; range, 36–85

Table 2 Postoperative Outcomes

	PIC group (n=30)	*Non-PIC group (n=70)*	*p value*
Operation time (min)	*255.7±50.3*	*239.2±57.6*	*0.248*
Distal anastomosis	*3.2±0.9*	*3.3±0.7*	*0.507*
CK-MB (ng/ml)	*19.8±34.2*	*10.6±11.1*	*0.189*
Postoperative bleeding/24 h (ml)	*678.0±582.8*	*628.1±369.4*	*0.668*
Transfusion	*14 (46.7)*	*25 (36.2)*	*0.375*
Ventilator time (h)	*33.5±45.3*	*16.7±6.4*	*0.003*
ICU stay (h)	*127.3±284.9*	*50.3±17.5*	*0.027*
Hospital stay (days)	*18.1±23.3*	*9.0±3.1*	*0.002*
Vasopressin use	*11 (36.7)*	*27 (39.1)*	*0.827*
IABP use	*3 (10.0)*	*0 (0)*	*0.026*

CK-MB, myocardial-bound CK; ICU, intensive care unit; IABP, intraaortic balloon pump. Other abbreviation see in Table 1.

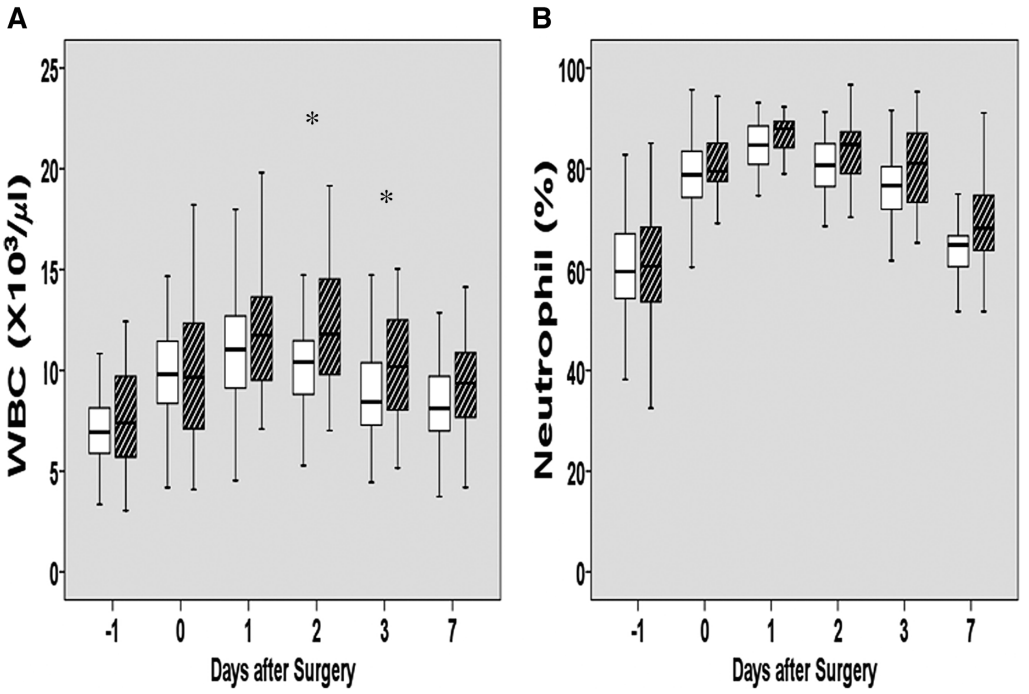

Fig 1. (A) Perioperative changes in white blood cell (WBC) counts according to development of postoperative inflammatory complications (PIC). (B) Perioperative changes in neutrophil percentage according to development of PIC (blank box, no PIC; shaded box, PIC; *p<0.05).

years) who underwent isolated primary OPCAB. Their preoperative ejection fraction was 55.8±0.5%, and their standard and logistic Euroscores were 2.96±2.56 and 3.45±6.91, respectively. Sixteen patients (16%) had already undergone percutaneous intraluminal catheter intervention. Seven patients were scored as New York Heart Association (NYHA) functional class I, 50 as NYHA class II, 32 as NYHA class III, and 11 as NYHA class IV. Eighty patients had triple vessel disease (Table 1). Preoperative clinical factors did not differ statistically between the PIC and non-PIC groups except age. The mean number of distal anastomosis was 3.2±0.7 (Table 2).

Perioperative Clinical Outcomes

One patient died within 30 days after surgery (1% surgical mortality rate), who experienced postoperative atrial fibrillation, aspiration pneumonitis, perioperative myocardial infarction, and cardiac arrest on the second postoperative day. Although the patient was under percutaneous cardiopulmonary support system, he died of low cardiac output syndrome. Multivariate analysis was not performed to assess death as a dependent variable, due to the small number of patients.

PIC occurred in 30 patients (postoperative pulmonary complications in 11, postoperative atrial fibrillation in 17, and wound infections in 4) at the median third postoperative day. Among the patients who experienced postoperative pulmonary complications, 6 experienced atelectasis, 2 experienced prolonged drainage of pleural effusion, 2 had pneumonia, and 1 had aspiration pneumonitis. All patients who experienced wound infections were categorized as superficial wound infection.

All patients were extubated between 6 and 20 h after arrival in the ICU; however, 2 patients required re-intubation and mechanical ventilatory support. One patient required a tracheostomy, and 3 patients (3%) needed postoperative intra-aortic balloon pump insertion. The mean duration of mechanical ventilatory support was 16.7±6.4 h for patients without PIC and 33.5±16.7 h for patients with PIC (p=0.003). Postoperative ICU stay was 50.3±17.5 h for patients without PIC and 127.3±285.0 h for patients with PIC

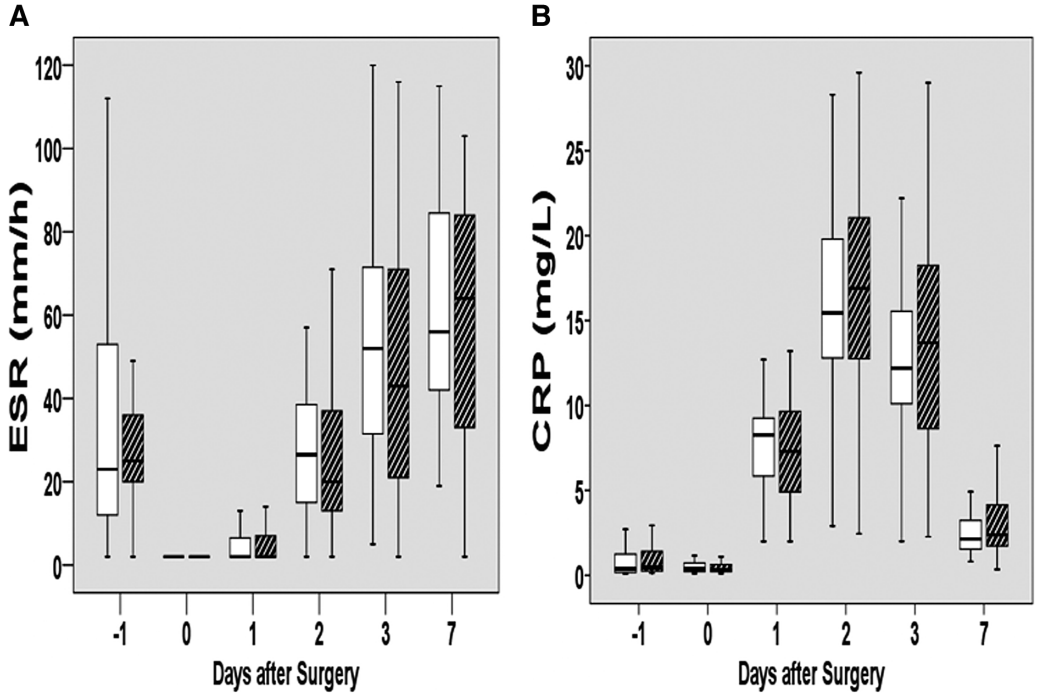

Fig 2. (A) Perioperative changes in erythrocyte sedimentation rate (ESR) according to development of postoperative inflammatory complications (PIC). (B) Perioperative changes in C-reactive protein (CRP) according to development of PIC (blank box, no PIC; shaded box, PIC).

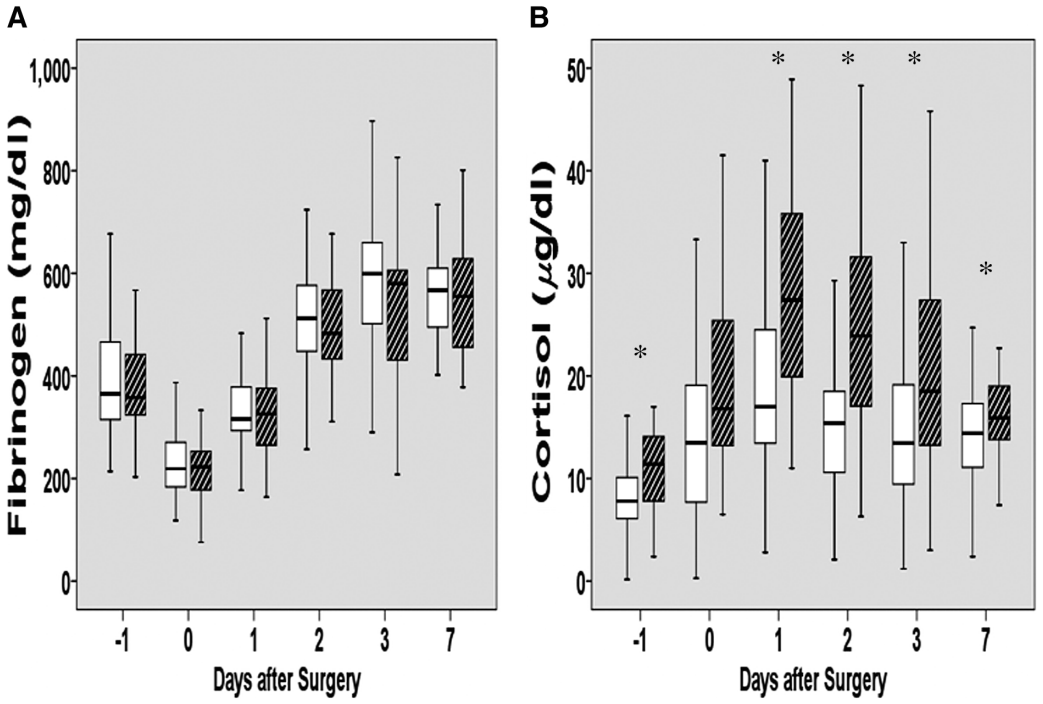

Fig 3. (A) Perioperative changes in fibrinogen according to development of postoperative inflammatory complications (PIC). (B) Perioperative changes in cortisol according to development of PIC (blank box, no PIC; shaded box, PIC; *p<0.05).

(p=0.027). The length of hospital stay was 9.0±3.1 days for patients without PIC and 18.1±23.3 days for patients with PIC (p=0.002) (Table 2).

Inflammatory Markers

Leukocyte counts rose immediate after surgery in both groups, reaching a maximum on the first postoperative day in the non-PIC group and on the second postoperative day in the PIC group. Thereafter, leukocyte counts decreased gradually but remained above baseline in both groups on the seventh postoperative day. Leukocyte counts on the second (12.4±3.1 vs 10.3±2.7×$10^3/\mu$l, p=0.003) and third (10.3±

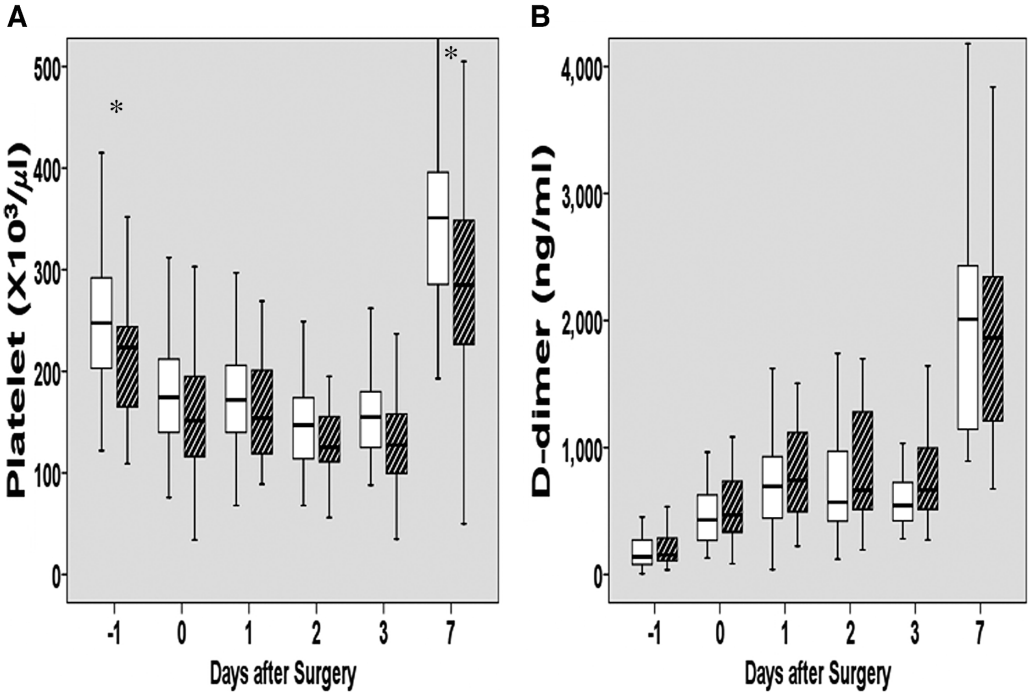

Fig 4. (A) Perioperative changes in platelet counts according to development of postoperative inflammatory complications (PIC). (B) Perioperative changes in D-dimer according to development of PIC (blank box, no PIC; shaded box, PIC; *p<0.05).

Table 3 Univariate and Multivariate Logistic Regression Analysis for Development of PIC After OPCAB

	Univariate analysis			*Multivariate logistic regression*		
	PIC group (n=30)	*Non-PIC group (n=70)*	*p value*	*OR*	*95%CI*	*p value*
Age (year)	*66.8±7.2*	*62.4±10.5*	*0.038*			
Preoperative day platelet ($10^3/\mu l$)	*213.5±61.5*	*254.7±86.6*	*0.02*			
Preoperative day cortisol ($\mu g/dl$)	*12.0±8.0*	*8.6±4.3*	*0.008*	*1.133*	*1.017–1.262*	*0.024*
1st postoperative day cortisol ($\mu g/dl$)	*30.3±15.3*	*19.2±8.5*	*0.001*	*1.084*	*1.031–1.140*	*0.001*

OPCAB, off-pump coronary artery bypass surgery; OR, odds ratio; CI, confidence interval. Other abbreviation see in Table 1.

2.8 vs 8.9±2.6×$10^3/\mu$l, p=0.026) postoperative days were significantly higher in the PIC group (Fig 1A).

Neutrophil counts rose immediately after surgery in both groups, reaching a maximum on the first postoperative day and decreasing gradually thereafter, but remaining above baseline in both groups on day 7. Neutrophil counts did not differ between the 2 groups (Fig 1B).

After an initial decline immediate after surgery, ESR rose gradually in both groups until day 7. ESR levels, however, did not differ significantly between the 2 groups (Fig 2A).

CRP declined immediately after surgery, increased on the first postoperative day, reached a maximum level on the second postoperative day and then declined gradually, but remained above baseline in both groups on day 7. CRP concentrations did not differ between the 2 groups (Fig 2B).

Fibrinogen concentrations declined immediately after surgery, increased on the first postoperative day, reached a maximum level on the third postoperative day, and then decreased gradually but remained high on day 7. Fibrinogen concentrations did not differ between the 2 groups (Fig 3A).

Cortisol concentration rose immediate after surgery in both groups, reaching a maximum on the first postoperative day and decreased gradually thereafter, but remained above baseline in both groups on day 7. Two-way analysis of variance for repeated measurements showed that the changes in cortisol concentrations were significant within each group over time and approached significance between the groups (p<0.05). Compared with the non-PIC group, cortisol concentrations in the PIC group were significantly higher preoperatively (12.0±8.0 vs 8.6±4.3μg/dl, p=0.008) and on postoperative days 1 (30.3±15.3 vs 19.2±8.5μg/dl, p=0.001), 2 (24.2±10.5 vs 15.4±7.3μg/dl, p=0.001), 3 (22.3±14.2 vs 14.3±7.1μg/dl, p=0.004) and 7 (17.0±6.2 vs 14.3±5.3μg/dl, p=0.042) (Fig 3B).

Coagulation Systems

Platelet counts decreased gradually, starting immediately after surgery until day 3, but recovered to baseline on day 7. Preoperative platelet count was significantly lower in the PIC group than in the non-PIC group (213.5±61.5 vs 254.7±86.6×$10^3/\mu$l, p=0.02) (Fig 4A).

D-dimer concentrations rose gradually, starting immediately after surgery until day 7. D-dimer concentrations did not differ significantly between the 2 groups (Fig 4B).

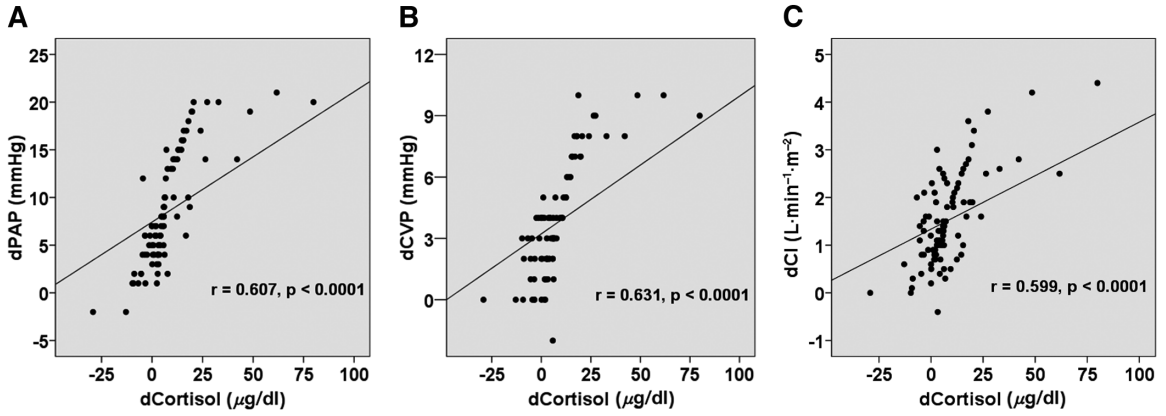

Fig 5. Relationship between intraoperative cortisol release and intraoperative hemodynamic changes. Intraoperative cortisol release was calculated as the difference between immediate postoperative and preoperative cortisol concentrations, and changes in hemodynamic data were calculated as the difference between each parameter during left circumflex artery anastomosis and just after induction of anesthesia. (A) Intraoperative cortisol release was correlated with intraoperative mean pulmonary artery pressure (PAP, r=0.607, p<0.0001). (B) Intraoperative cortisol release was correlated with central venous pressure (CVP, r=0.631, p<0.0001). (C) Intraoperative cortisol release was negatively correlated with cardiac index (CI, r=–0.599, p<0.001).

Risk Factors for PIC

Since earlier prediction of PIC after OPCAB might be very important, we assessed risk factors before and immediately after surgery. Univariate analysis showed that age (p=0.038), preoperative platelet count (p=0.02) and preoperative cortisol concentation (p=0.008), and day 1 postoperative cortisol concentration (p=0.001) were associated with development of PIC.

Multivariate logistic regression analysis showed that higher preoperative cortisol concentration (12.0±8.0 vs 8.6±4.3 μg/dl, p=0.024), and higher cortisol concentration on postoperative day 1 (30.3±15.3 vs 19.2±8.5 μg/dl, p=0.001) were significantly associated with the development of PIC (Table 3).

Intraoperative Hemodynamic Changes

We also assessed the relationship between intraoperative cortisol release and intraoperative hemodynamic changes, including mean arterial pressure, heart rate, central venous pressure, mean pulmonary artery pressure, cardiac index, and mixed venous O_2 saturation. Intraoperative cortisol release was calculated as the difference between immediate postoperative and preoperative cortisol concenrations, and changes in hemodynamic variables were calculated as the difference between each parameter during left circumflex artery anastomosis and just after induction of anesthesia.

Intraoperative cortisol release was well correlated with intraoperative mean pulmonary artery pressure (r=0.628, p<0.0001), central venous pressure (r=0.633, p<0.0001), and cardiac index (r=–0.516, p=0.001) (Fig 5). Also, we compared the intraoperative cortisol release between the 2 groups (15.1±14.6 μg/dl in the PIC group, and 7.7±14.1 μg/dl in the non-PIC group, p=0.032).

Discussion

On-pump coronary artery bypass surgery (ONCAB) has risks of mortality (2–5%), stroke (2%), transfusions (30–90%), atrial fibrillation (30%), and neurocognitive dysfunction (50–75%).[17–20] Comparisons of OPCAB and ONCAB have shown that OPCAB is associated with improvements in short-term outcomes, including atrial fibrillation, blood transfusion, and length of hospital stay in patients not selected for risk.[21] Despite these advantages, many PIC can occur after OPCAB, and these are associated with prolonged hospital stay and eventually surgical mortality. Thus, accurate prediction of PIC in patients with coronary artery obstructive disease is very important. Patients with coronary artery disease who undergo evaluation for OPCAB usually have a history of diabetes, hypertension, smoking, and/or chronic obstructive pulmonary disease with impaired lung function, putting them at increased risk for development of PIC. Therefore, in addition to assessing the clinical status of coronary lesions, physiological assessment of these patients is very important. However, little is known about the factors associated with overall morbidity and mortality after OPCAB.

We have shown here that increased cortisol concentrations preoperatively and on the first postoperative day are independent predictors for development of PIC after OPCAB. Cortisol is an inflammatory marker and acute stress hormone that is synthesized by the adrenal gland and released in large amounts into the circulation, primarily in response to interleukin-6 stimulation, during systemic inflammation. Elevated serum cortisol can affect coagulability, blood viscosity and rheology, platelet aggregation, and endothelial function, all of which might induce microthrombosis in the collateral capillaries and ischemic changes, and make patients vulnerable to ischemia, inflammation, and infection, especially after surgery. Therefore, measurement of serum cortisol concentrations might provide a non-invasive method of identifying ongoing inflammation and tissue ischemia.

Despite avoiding CPB, OPCAB is associated with decreases in PaO_2, pulmonary compliances, and pulmonary function similar to on-pump CABG, which might lead to delayed extubation and necessitate strategies to minimize postoperative pulmonary impairments.[22,23] In addition, temporary interruption of the coronary blood flow for bloodless anastomotic conditions might cause various degrees of myocardial damage. Although the period of 1 target vessel occlusion is usually approximately 15 min, multiple grafts might be associated with cumulative ischemia-reperfusion myocardial injury.[24,25]

Compared with the controlled systemic flow conditions of CPB, cardiac manipulation during OPCAB to expose target coronary arteries can lead to significant hemodynamic impairment, with transient drops in cardiac output, despite relative preservation of the mean arterial pressure. Hemodynamic deterioration is primarily caused by right ventricular dysfunction, resulting from compression of the right heart chambers against the surrounding fibrous pericardium and pleura.[26] These hemodynamic changes are more pronounced when extensive cardiac manipulation is required to expose a target vessel on the posterolateral aspect of the heart, and are generally reversible once the heart is replaced in its normal position. Thus, in terms of stress hormone response, the benefits conferred by avoiding CPB might be negated by the cumulative hemodynamic stress of OPCAB surgery.

We found significant correlations between intraoperative cortisol release and intraoperative hemodynamic changes. Furthermore, we tested if intraoperative cortisol release could be a significant risk factor for development of PIC. Intraoperative cortisol release was 15.1±12.6 μg/dl in the PIC group, and 7.7±14.1 μg/dl in the non-PIC group (p=0.032). As a result, summation of intraoperative hemodynamic changes affected intraoperative cortisol release, and then it could affect the development of PIC. Because intraoperative hemodynamics during OPCAB are controlled by the cardiovascular surgeon and by experienced cardiac anesthesiologists, close cooperation between them during OPCAB can minimize intraoperative hemodynamic changes, intraoperative cortisol release, and PIC.

Preoperative serum cortisol is a surrogate measurement of the level of preoperative stress and inflammatory response. In contrast, serum cortisol concentration on the first postoperative day is a summation of the cumulative effect of preoperative cortisol, intraoperative cortisol release, and cortisol release during the first 12 h postoperatively.

We hypothesized that perioperative serial measurements would provide a more accurate picture of the cumulative effect of surgery on the hormonal milieu, enabling a valid comparison between the PIC and non-PIC group. Unexpectedly, however, we found that immediate postoperative serum cortisol concentration did not differ between the 2 groups. Serum cortisol concentration immediately after surgery was thought difficult to interpret in the context of hemodilution during OPCAB. This issue has been controversial, with most authors suggesting that no correction should be made for hemodilution, as the concentration of a hormone in a target organ is directly affected by its concentration in the serum rather than the total amount in the intravascular fluid. However, we cannot assess the effect of hemodilution. This confounding factor is less relevant beginning on postoperative day 1, when the body has begun to compensate by redistributing the excess volume between its fluid compartments. In addition, the serum concentration of cortisol undergoes diurnal variation, with the highest levels present in the early morning, and the lowest levels present around midnight, 3–5 h after the onset of sleep. We measured immediate postoperative cortisol in arterial blood at around 14.00–16.00 h, at which time cortisol level was lower than at 07.00–09.00 h. Thus, we could not correct the immediate postoperative cortisol concentration because of the hemodilution effect and diurnal variation.

In conclusion, we have shown here that patients with PIC after OPCAB have significantly increased cortisol concentrations, preoperatively and on the first postoperative day. We also found that intraoperative cortisol release was significantly correlated with intraoperative hemodynamic changes. Our findings suggest that the neurohormonal environment and inflammatory response during and after beating-heart surgery should be further explored.

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