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Factors Affecting the Postoperative Outcome in Adult Cardiac Surgery with Cardiopulmonary Bypass

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We defined factors affecting the postoperative outcome in adult cardiac surgery with cardiopulmonary bypass (CPB). Thirty-two adult patients scheduled for elective cardiac surgery participated in this study. Levels of leukocyte, glutamic oxaloacetic transaminase (GOT), troponin-I (cTNI), interleukin-6 (IL-6), D-dimer and neuron-specific enolase (NSE) were significantly elevated, whereas platelet count declined in cardiac surgery with CPB. GOT and D-dimer levels at CPB-off each had a positive significant correlation significantly with 24 hrs-bleeding, total bleeding, mechanical ventilatory assist time, ICU stay time and length of hospitalization. BUN levels at CPB-off were directly related to total bleeding, mechanical ventilatory assist time, ICU stay time and length of hospitalization. Platelet count at CPB-off was inversely related to mechanical ventilatory assist time, ICU stay time and length of hospitalization. Creatinine concentration at CPB-off interrelated positively with mechanical ventilatory assist time and ICU stay time. NSE levels at CPB-off had a positive relationship with postoperative 24 hrs-bleeding. The length of hospitalization was prolonged proportionally to the elevation of cTNI levels in cardiac surgery. Aortic cross-clamping and total CPB times also related with increase of 24 hrs and total bleeding volumes and the length of hospitalization. IL-6 and ET-1 had no mutual relation with any postoperative outcome. These data suggest that GOT, BUN, creatinine, D-dimer and platelet levels are the most important factors affecting postoperative outcomes and patient's recovery in adult cardiac surgery with CPB.

Key words : Adult cardiac surgery, cardiopulmonary bypass, postoperative outcomes

Introduction

Despite improved surgical techniques and heart-lung devices, complications have an adverse and variable influence on the outcomes of cardiac surgery with cardiopulmonary bypass (CPB). Although CPB is fundamental for heart operations, it is associated with substantial postoperative morbidity and/or mortality. Exposure of blood to artificial surfaces such as oxygenator and heart-lung system leads to activations of leukocyte, complement, coagulation, cytokine, fibrinolytic, and kallikrein cascades [1,5,12]. These phenomenon, so-called systemic inflammatory responses, may affects patients' recovery after cardiac surgery. However, many researchers have argued about the factors affecting the postoperative outcomes after cardiac surgery with CPB. Especially, in recent years there has been considerable interest in controlling hospital costs. Prolonged intensive care unit (ICU) stay and hospitalized days caused by postoperative outcomes are the main reasons for high hospital costs.

The purpose of our study was to assess those factors that affect the postoperative outcome after adult cardiac surgery with CPB. We considered postoperative mechanical ventilatory assist time, 24 hrs- and total-bleeding volumes, and the length of ICU and hospital stay as postoperative outcomes.

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Materials and Methods

Patients

Thirty-two adult patients scheduled for elective cardiac surgery participated in this study. The criteria of exception in the present study were patients suffering cerebral problems, hematological, immunological, liver or renal disorders.

Cardiopulmonary bypass (CPB)

In CPB for their cardiac surgery, nonpulsatile five-head

roller pump (Stökert Co., Germany), membrane oxygenator (Baxter Healthcare Co., America), arterial filter (Baxter Healthcare Co., America) and circuit tube (Gish Co., America) were utilized. Before the application of CPB system to the patients, heparin was administered via CVP (central venous pressure) line for maintaining above 500 sec of ACT (activated clotting time). The priming solution consisted of Hartmann solution, 15% mannitol (6 ml/kg), sodium bicarbonate (1 meq/kg), calcium chloride (0.6 g), ascorbic acid (1.0 g) and antibiotics (3 g) and was primed into CPB system for hemodilution (adjusting 20-25% of hematocrit). Cardioplegic solution (4°C) was infused into aortic root for heart arrest and myocardial protection every 20 min. Moderate hypothermic CPB (28-32°C of nasopharyngeal temperature) was applied with 2.0-2.4 l/min/m^2 of perfusion rate. Mean arterial blood pressure (MBP) and $PaCO_2$ (partial pressure of carbon dioxide) were kept with 50-70 mmHg and 35-40 mmHg, respectively during CPB. After CPB-weaning, heparin was neutralized by protamine (1.5 × administered heparin) administration.

Blood sampling and sample treatment

Blood samples were taken from radial artery on the preoperative, intraoperative and postoperative periods (expression as Pre-CPB, CPB-10m and CPB-off, respectively). 2 ml of blood was analyzed for the leukocyte and platelet counts. The rest of the blood sample (8 ml) was centrifuged (3,000 rpm for 10 min) and the separated plasma was frozen at -70°C until the glutamic oxaloacetic transaminase (GOT) and glutamic pyrubic transaminase (GPT) (liver function marker), blood ureanitrogen (BUN) and creatinine (renal function marker), troponin-I (cTNI, cardiac marker), interleukin-6 (IL-6, proinflammatory cytokine), neuron-specific enolase (NSE, brain marker), endothelin-1 (ET-1, vascular marker), and D-dimer (fibrinolytic activation marker) assay were performed.

Assay of biochemical and organ markers assay

All above mentioned parameters were analyzed on the three periods (Pre-CPB, CPB-10 min and CPB-off). GOT, GPT, BUN and creatinine levels were measured by chemistry autoanalyzer (Bayer, Japan) with each commercial kits (Bayer, Japan). NSE (immunoradiometric assay) and cortisol (RIA method) concentrations were measured by gamma-counter (Packard Co., America) with ELISA-NSE kit (CIS Bio international, America) and Coat-A-Count cortisol kit (DPC, America), respectively. IL-6 level (EIA method) was determined by Emax precision microplate reader (Molecular Device, America) with Quantikine HS human IL-6 kit (R&D System, America). ET-1 concentration was detected by Luminometer (Digene, America) with QuantiGlo human ET-1 kit (R&D System, America). cTNI level was measured by Immunology autoanalyzer (Bayer, America) with cardiac troponin-I kit (Bayer, America).

Indices for evaluating postoperative outcome

We assessed postoperative mechanical ventilatory assist time, 24 hr- and total-bleeding volumes, and the length of ICU and hospital stay for postoperative outcomes.

Statistical analysis

Data are presented as mean±SE (standard error). All parameters were statistically analyzed with repeat measure ANOVA (SAS program). The relationship between each variable and the index of postoperative outcome was assessed by Pearson's correlation. Statistical significance was attributed to p values lower than 0.05.

Results and Discussion

Characteristics of study population

Tables 1 and 2 show the characteristics of study population. Patients had congenital or acquired heart diseases. Aortic cross-clamping and total CPB time were 87.37±3.20 hrs and 115.53±3.93 hrs, respectively (Table 1).

Changes in hematology

Leukocyte count at CPB-10m decreased, while at CPB-off

Table 1. Demographic characteristics of study population

Characteristics	Values
Total case number	32
Gender ratio (male:female)	20:12
Age (years)	52.17±4.08
Weight (kg)	62.85±3.19
Body surface area (m^2)	1.65±0.02
Perfusion rate (l/min/m^2)	2.20±0.00
NT (°C)	30.12±0.05
ACC time (min)	87.38±2.43
Total CPB time (min)	115.63±7.62

Data are expressed as mean±standard error (SE).
Abbreviation: NT, nasopharyngeal temperature; ACC, aortic cross-clamping; CPB, cardiopulmonary bypass.

Table 2. Operative procedures in study population

Procedure of operation	Number of cases
Repair of atrial septal defect (ASD)	2
Mitral valve replacement (MVR)	7
Aortic valve replacement (AVR)	7
Double valve replacement (DVR)	2
MVR + Tricuspid valve annuloplasty (TVA)	6
DVR + TA	2
AVR + Coronary artery bypass grafting (CABG)	1
CABG	1
ASD + Tricuspid valve replacement	1
Left atrial myxoma (LAM)	1
LAM + TVA	1
Repair of valsalva	1
Total	32

it increased compared with baseline (Pre-CPB) (p=0.02 and p=0.01, respectively, Table 3). Platelet counts were lower than baseline on CPB-10m and CPB-off (p=0.013 and p=0.04, respectively, Table 3). These findings indicate that CPB system causes inflammatory reactions and platelet activation and aggregation due to the oxygenator and sucker pump [1-4]. D-dimer level at CPB-off (p=0.04) was significantly higher than that of Pre-CPB (Table 3). Increased D-dimer level due to CPB is recognized as activation of fibrinolytic system and may contribute to postoperative bleeding.

Biochemistry

GOT level at CPB-off was higher than that of Pre-CPB (p=0.04, Table 4), but not changed in GPT, suggesting impairment of liver function attributable to CPB. In contrast, BUN and creatinine concentrations, and the renal function marker, were not significantly changed during CPB (p>0.05, Table 4).

Table 3. Changes of hematological variables during cardiac surgery with CPB

Variable	Sampling point		
	Pre-CPB	CPB-10m	CPB-off
Leukocyte (no./μl)	5,279.33±198.31	3,288.00±200.10*	9,013.70±852.48*
Platelet ($\times 10^3$/μl)	199.97±65.22	96.47±43.97*	109.77±41.09*
D-dimer (μg/ml)	0.18±0.03	0.19±0.02	0.39±0.06*

Data are expressed as mean±SE.
*, p<0.05 (compared with Pre-CPB).

Table 4. Changes od biochemical variables during cardiac surgery with CPB

Variable	Sampling point		
	Pre-CPB	CPB-10m	CPB-off
GOT (U/l)	22.07±13.18	18.17±8.7*	39.37±21.49*
GPT (U/l)	18.03±10.79	15.13±7.54	16.17±6.47
BUN (mg/dl)	14.93±4.39	13.01±3.65	13.54±3.53
Creatinine (mg/dl)	0.92±0.17	0.86±0.15	0.87±0.17

Data are expressed as mean±SE.
*, p<0.05 (compared with Pre-CPB).
Abbreviation: GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyrubic transaminase; blood ureanitrogen (BUN).

Organ markers

cTNI, IL-6 and NSE levels were elevated in CPB-10m (p=0.02, p=0.04 and p=0.03, respectively) and CPB-off (p=0.01, p=0.02 and p=0.02, respectively) compared with that of Pre-CPB (Fig. 1). cTNI, as a part of the tropomyosin complex in myocardium, is released when cardiac damage occurs. cTNI represents a major marker in the evaluation of myocardial injury in patients after cardiac surgery [8,10,21]. Although cardioplegic solution is used for myocardial protection, some degree of myocardial injury takes place. Proinflammatory cytokine IL-6 is secreted from a number of cells, including macrophages, activated T-lymphocytes, endothelial cells, fibroblast and ischemic myocytes [13]. During CPB, the contact of the patient's blood to artificial surfaces of heart-lung machine system induces increased IL-6 production, which causes systemic inflammatory responses and multi-organ dysfunctions,

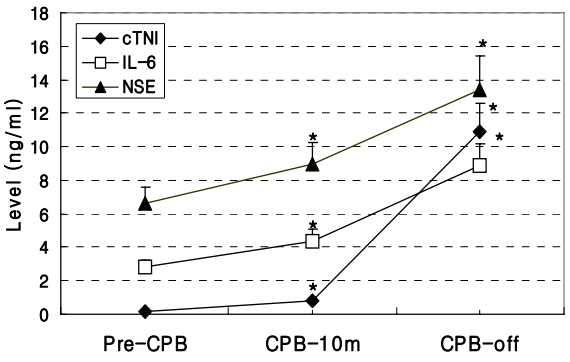

Fig. 1. Changes in cTNI, IL-6 and NSE levels in the cardiac surgery with cardiopulmonary bypass (CPB). All variables in CPB-10m and CPB-off were significantly elevated compared with Pre-CPB (*, p<0.05). Pre-CPB, before operation with CPB; CPB-10m, 10 min after initiation of operation with CPB; CPB-off, immediately after the end of cardiac operation with CPB.

so-called "postperfusion syndromes". NSE (neuron-specific enolase) with 78 kDa of molecular weight is a isoenzyme (γγ-subunits) of glycolytic enzyme enolase (2-phospho-D-glycerate hydrolase) that exists in neuron and neuroendocrine. It is high specific for neurons and is excreted into cerebrospinal fluid, cerebral circulation and circulatory blood if there is neuron damages [2,6,17-20]. The increase in NSE level in this study potentially implies that CPB may lead to reversible neuron injury [3,4,11]. Endothelin-1 (ET-1) level at CPB-10m slightly decreased and at CPB-off it tended to elevate but not significantly compared with that of Pre-CPB (p>0.05, Fig. 2). Endothelin with 21 amino acid residues is a potent vasoconstrictor polypeptide that possesses a variety of ,biological effects including the control of vascular tone [16,22]. It consists of three isoform, endothelin-1, endothelin-2 and endothelin-3. ET-1 is selectively derived from the heart and lungs. In addition to cardiogenic shock, acute myocardial infarction, congestive heart failure, hypertension and severe cardiovascular stress, cardiopulmonary bypass brings about vessel injuries and raises circulatory ET-1 levels in blood [7,9,14,23]. We found no significant changes in ET-1 levels during CPB, suggesting that our CPB protocol did not generate vascular damage.

Postoperative outcomes

Postoperative outcomes are summarized in Table 5. Bleeding volume 24 hr after cardiac surgery was 562.67±49.24 ml and postoperative total bleeding volume was 1039.67±60.99 ml. Postoperative mechanical ventilatory assist and ICU stay times were 19.78±2.54 hrs and 113.43±13.04 hrs, respectively. The length of hospitalization was 23.47±0.92 days.

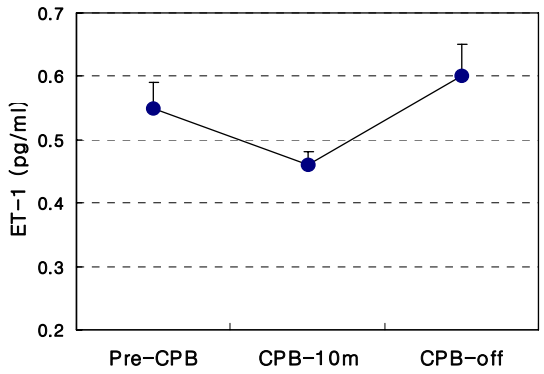

Fig. 2. Endotheline-1 (ET-1) levels in the cardiac surgery with cardiopulmonary bypass (CPB). There were not significant changes at any sampling points (p>0.05).

Table 5. Postoperative outcomes in study population

Variable	Values
24 hrs-bleeding volume (ml)	561.67±49.24
Total bleeding volume (ml)	1,039.67±60.99
MVAT (hr)	19.78±2.54
ICU stay (hr)	113.43±13.04
Hospitalization (day)	23.47±0.92

Data are expressed as mean±standard error (SE).
Abbreviation: MVAT, mechanical ventilatory assist time; ICU, intensive care unit.

Table 6. Correlation of variable to postoperative outcome

Variable	Correlation coefficient				
	24-BL	T-BL	MVAT	ICU-stay	Hospitalization
GOT (r)	**0.40**	**0.40**	**0.46**	**0.43**	**0.43**
(p value)	**0.02**	**0.02**	**0.01**	**0.02**	**0.02**
GPT (r)	0.28	0.26	0.24	0.28	0.13
(p value)	0.14	0.17	0.20	0.14	0.49
Creatinine (r)	-0.01	0.08	**0.46**	**0.38**	0.14
(p value)	0.97	0.66	**0.01**	**0.04**	0.47
BUN (r)	0.20	**0.43**	**0.66**	**0.63**	**0.61**
(p value)	0.29	**0.02**	**0.000**	**0.000**	**0.000**
cTNI (r)	0.26	0.30	0.25	0.19	**0.35**
(p value)	0.17	0.11	0.18	0.31	**0.05**
IL-6 (r)	-0.28	-0.30	0.02	-0.04	-0.25
(p value)	0.13	0.10	0.90	0.85	0.18
ET-1 (r)	-0.09	-0.16	-0.09	-0.06	-0.10
(p value)	0.62	0.43	0.60	0.73	0.57
D-dimer (r)	**0.51**	**0.64**	**0.68**	**0.64**	**0.69**
(p value)	**0.004**	**0.000**	**0.000**	**0.000**	**0.000**
NSE (r)	**0.43**	0.30	0.16	0.084	0.19
(p value)	**0.02**	0.10	0.37	0.65	0.29
Leukocyte (r)	-0.14	-0.20	-0.09	-0.12	-0.02
(p value)	0.45	0.28	0.62	0.53	0.90
Platelet (r)	-0.05	-0.21	**-0.35**	**-0.38**	**-0.38**
(p value)	0.79	0.27	**0.05**	**0.03**	**0.04**
ACC (r)	**0.45**	**0.47**	0.27	0.24	**0.47**
(p value)	**0.01**	**0.01**	0.15	0.20	**0.01**
T-CPB (r)	**0.37**	**0.43**	0.26	0.20	**0.46**
(p value)	**0.04**	**0.02**	0.17	0.28	**0.01**

r, correlation coefficient.
Abbreviation: 24-BL, postoperative 24 hrs-bleeding volume; T-BL, postoperative total bleeding volumes; MVAT, mechanical ventilatory assist time; ICU, intensive care unit; ACC, aortic cross-clamping time; T-CPB, total cardiopulmonary bypass time.

Correlation between each parameter and postoperative outcome

Table 6 shows the relationship between each parameter

and postoperative outcome. GOT and D-dimer levels at CPB-off each had a positive significant correlation with 24 hrs-bleeding, total bleeding, mechanical ventilatory assist time, ICU stay time or length of hospitalization. BUN levels at CPB-off was directly related to total bleeding, mechanical ventilatory assist time, ICU stay time or length of hospitalization. Platelet count at CPB-off was inversely related to mechanical ventilatory assist time, ICU stay time or length of hospitalization. Creatinine concentration at CPB-off interrelated positively with mechanical ventilatory assist time and ICU stay time. NSE levels at CPB-off had a positive relationship with postoperative 24 hrs-bleeding. The length of hospitalization was prolonged proportionally to the elevation of cTNI levels in cardiac surgery. Aortic cross-clamping and total CPB times were also related with the increase of 24 hrs and total bleeding volumes and the length of hospitalization. Nevertheless, IL-6 and ET-1 had no mutual relation with any postoperative outcomes. In conclusion, these results indicate that some damages in liver (GOT) and renal functions (BUN and creatinine), fibrinolytic activation (D-dimer) and decreased platelet count attributable to CPB are the most important factors affecting postoperative outcomes and patient's recovery. Other variables including aortic cross-clamping and total CPB times also influence the recovery after adult cardiac surgery.

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초록 : 심폐바이패스를 이용한 성인 심장수술 시 환자회복에 영향을 미치는 인자

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본 연구는 심폐바이패스를 이용한 성인 심장수술 시 수술 후 환자의 회복 결과에 영향을 미치는 인자들을 규명하기 위해 시행하였다. 성인 심장수술 환자 32명을 대상으로 하여 연구하였다. 심장수술 시 밸혈구 수, GOT, troponin-I (cTNI), interleukin-6 (IL-6), endothelin-1 (ET-1), D-dimer, neuron-specific enolase (NSE) 등의 혈장농도는 유의하게 증가한데 비해 혈소판 수는 감소하였다. 수술 직후 GOT 및 D-dimer 농도와 24 시간 및 총출혈량, 기계호흡보조 시간, 중환자실 치료기간, 재원일수와 각각 양의 상관성이 있었다. 혈소판 수와 기계호흡보조 시간, 중환자실 치료기간, 재원일수와 각각 음의 상관관계가 있었다. Creatinine 농도와 기계호흡보조 시간, 중환자실 치료기간 사이에 양의 상관성이 있었다. NSE 농도와 24 시간 출혈량 사이에 양의 상관관계를 보였다. cTNI 농도와 재원일수 간에 양의 상관성이 있었다. 대동맥 교차차단 및 총심폐바이패스 실시 시간과 24 시간 및 총 출혈량, 재원일수 사이에 양의 상관관계를 나타내었다. 결론적으로 본 연구의 결과들은 심폐바이패스를 적용한 성인 심장수술 시 수술 후 환자의 결과와 회복에 영향을 미치는 가장 중요한 변수는 수술 종료 직후(CPB-off)의 GOT, BUN, creatinine, D-dimer 등의 농도와 혈소판 수임을 시사하고 있다.