Study on the Relationship of APACHE III and Levels of Cytokines in Patients with Systemic Inflammatory Response Syndrome after Coronary Artery Bypass Grafting

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The aim of this study was to explore the relationship and interpret the clinical importance of acute physiology and chronic health evaluation III (APACHE III) and levels of cytokines in patients with systemic inflammatory response syndrome (SIRS) after coronary artery bypass grafting (CABG) with or without cardio-pulmonary bypass (CPB) to see if they are beneficial for evaluating the seriousness of SIRS. The data suggested that the APACHE III score and levels of interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), interleukin-1 beta (IL-1 β), and soluble interleukin-2 receptor (sIL-2R) were significantly higher after conventional CABG (CCABG) than after off-pump coronary artery bypass grafting (OPCAB) ($p < 0.05$). With an increase in the APACHE III score, the levels of IL6, IL8, TNF- α , IL-1 β , and sIL-2R and the morbidity of multiple organ dysfunction syndrome (MODS) increased gradually ($p < 0.01$), while the level of IL2 decreased ($p < 0.01$). Stepwise regression analysis showed that IL-1 β , IL6, IL8, and sIL-2R levels had significant influences on the APACHE III score ($p < 0.05$). The APACHE III score and levels of IL6, IL8, TNF- α , IL-1 β , and sIL-2R were significantly higher in the MODS group than in the non-MODS group ($p < 0.05$), but the level of IL2 was significantly lower in the MODS group ($p = 0.04$). In conclusion, despite comparable surgical trauma, we believe that CPB is one of the most important factors responsible for stimulating an inflammatory response. SIRS after OPCAB was clearly mitigated compared with CCABG. Determination of the APACHE III score and plasma IL-1 β , IL6, IL8 and sIL-2R concentrations might be helpful for evaluating the severity of SIRS following CABG and making a prognosis.

Key words systemic inflammatory response syndrome; cardio-pulmonary bypass; cytokine

Systemic inflammatory response syndrome (SIRS) describes the clinical presentation of patients with systemic activation of the inflammatory response from any underlying cause. SIRS is a common problem in acute medical and surgical practice and an important cause of morbidity and mortality. As a consequence of SIRS, patients may develop acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS). SIRS refers to a systemic, whole body, non-localized response. This response, which occurs to some degree in most patients undergoing coronary artery bypass graft surgery (CABG), has the potential to affect all tissues and vital organs. We have been attempting to explore the relationship and interpret the clinical importance of acute physiology and chronic health evaluation III (APACHE III) and cytokine levels in patients with SIRS after coronary artery bypass grafting (CABG) with or without cardio-pulmonary bypass (CPB) to determine if they are beneficial for evaluating the seriousness of SIRS with the goal of decreasing postoperative complications and increasing the survival rate after CABG.

MATERIALS AND METHODS

Patients The original selection criterion was that the patient had SIRS in the first 24 h after CABG. According to the American College of Chest Physicians and the Society of Critical Care Medicine, a diagnosis of SIRS is based upon two or more of the following clinical presentations¹⁾: rapid heart rate (tachycardia, heart rate > 90 /min); low or high body temperature (< 36 or > 38); high respiratory rate (tachypnea, respiratory rate > 20 breaths per minute), and white blood cell count < 4000 cells/mm³ or > 12000 cells/mm³. Patients who were included in our research had no significant impairment of renal or liver function, no acute infection, no cardiac valve diseases, no severe myocardial dysfunction (EF $< 30\%$), and did not have any malignant tumors or immunodeficiency disease before CABG. Patients who had to be switched from an off-pump to pump coronary artery bypass grafting due to various causes during surgery were excluded. The criteria for a diagnosis of MODS have been described in the literature.²⁾

From July 2004 to March 2005, 65 patients who had undergone elective CABG were randomly divided into a CABG

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with CPB group (CCABG, 31 cases) and a CABG without CPB group (OPCAB, 34 cases) using a random number table. No patient was changed from off-pump to pump coronary artery bypass grafting. Two patients in the CCABG group were excluded due to chronic renal dysfunction and cardiac valve disease, respectively. Forty-two out of 63 cases were included in the study. The demographic and clinical data of the patients are outlined in Table 1.

Study Protocol The patients were divided into group A (≤ 60), group B (61–90), or group C (> 90) according to the APACHE III score,³⁾ and into an MODS group and non-MODS group according to the signs of multiple organ dysfunction syndrome (MODS)²⁾ within 24 h after inclusion in the study. The acute physiology and chronic health evaluation III score was assessed using the worst clinical parameters⁴⁾ within 24 h after an operation. Blood samples (4.5 ml, citrated) for cytokine measurement were drawn 24 h after an operation, coagulated, and the plasma was frozen at -80°C until analysis. IL6, IL8, TNF- α , IL-1 β , and IL2 were measured using a standard commercial assay (Ke Mei Dong Ya Biological Technology Limited Company, Beijing) by staff blind to all subject data. The sIL-2R ELISA assay was obtained from Jing Mei Biological Technology Limited Company.

Statistical Analysis Statistical analysis was performed using an SPSS10 statistical software package. Continuous variables are presented as the mean $\pm$ standard deviation. The two groups were compared using the unpaired *t*-test. Chi-square analysis was used to compare quantitative data. Spear-

man's rank correlation and linear regression analysis were used to evaluate the relationship between the APACHE III score and the levels of cytokines. All *p* values < 0.05 were considered to indicate statistical significance.

RESULTS

As noted in Table 1, there were no significant differences in gender, age, body weight, preoperative left ventricular ejection fraction (LVEF), number of grafts, transfusion volume, and drainage volume between the CCABG group and the OPCAB group. Patients in the CCABG group, however, had longer ICU stay, mechanical ventilation, and fever durations after surgery than those in the OPCAB group. Although the rate of MODS and the frequency of SIRS were higher in the group CCABG than in the group OPCAB, there were no statistical differences between the two groups, which was most likely due to the small sample size.

A comparison of the APACHE III scores and levels of cytokines between the CCABG group and the OPCAB group is shown in Table 2. The APACHE III score and levels of IL6, TNF- α , IL-1 β , and sIL-2R were significantly higher after CCABG than after OPCAB, while the levels of IL2 and IL8 were lower after CCABG than after OPCAB.

A comparison of cytokine levels and morbidity of MODS among groups A, B, and C based on the APACHE III score is presented in Table 3. As the APACHE III score increased, the levels of IL6, IL8, TNF- α , IL-1 β , and sIL-2R and the morbidity of MODS increased gradually, while level of IL2

Table 1. Demographic and Clinical Data of Patients

Variable		CCABG (<i>n</i> =20)	OPCAB (<i>n</i> =22)	<i>p</i> value
Before operation	Gender (Male/Female)	15/5	18/4	> 0.05
	Age (years)	64.52 ± 8.14	67.81 ± 7.77	> 0.05
	Body weight (kg)	68.40 ± 7.53	70.31 ± 6.44	> 0.05
	LVEF	0.54 ± 0.08	0.53 ± 0.09	> 0.05
During operation	Number of grafts	3.55 ± 0.76	3.14 ± 0.71	> 0.05
	Pump time (min)	114 ± 21.40	0	< 0.01
	Aortic cross-clamp time (min)	53.35 ± 19.02	0	< 0.01
	Duration of surgery (min)	290.25 ± 63.17	230 ± 50.40	< 0.05
After operation	Extubation time (h)	34.15 ± 31.77	17.50 ± 12.99	< 0.05
	Fever time (d)	3.40 ± 2.87	1.68 ± 0.99	< 0.05
	Drainage volume (ml)	641.60 ± 279.64	487.95 ± 275.71	> 0.05
	Transfusion volume (ml)	920.00 ± 653.41	772.73 ± 542.64	> 0.05
	Atrial fibrillation after CABG	4	2	> 0.05
	Frequency data of SIRS	20/29	22/34	> 0.05
	Multiple organ dysfunction	6	2	> 0.05
	Stay at the ICU (d)	2.93 ± 2.05	2.14 ± 1.04	< 0.05
	MODS score	7.84 ± 3.38	5.85 ± 2.83	< 0.05
	Sternal infection	1	0	
	Reoperation for bleeding	1	1	
	Continuous blood purification	1	0	
	Survival (%)	100	100	

Table 2. Comparison of the APACHE III Score and Levels of Cytokines between CABG and OPCAB Groups

Group	<i>n</i>	APACHE III	MODS	IL6 (pg/ml)	IL8 (pg/ml)	TNF- α (pg/ml)	IL-1 β (pg/ml)	IL2 (IU/ml)	sIL-2R (U/ml)
CCABG	20	73.9 ± 20.96	6	667.5 ± 183.97	14.4 ± 8.58	44.3 ± 25.33	30.8 ± 14.20	10.4 ± 5.08	597.2 ± 459.33
OPCAB	22	57.9 ± 20.75	2	525.8 ± 154.98	17.8 ± 11.29	25.1 ± 18.01	18.1 ± 9.42	16.6 ± 10.68	377.5 ± 212.09
<i>T</i> value		2.483		2.709	-1.081	2.860	3.446	-2.454	2.021
<i>p</i> value		0.017	> 0.05	0.01	0.286	0.007	0.001	0.02	0.05

Table 3. Comparison of Levels of Cytokines and Morbidity of MODS among Groups A, B, and C Based on the APACHE III Score

Group	n	MODS	IL6 (pg/ml)	IL8 (pg/ml)	TNF- α (pg/ml)	IL-1 β (pg/ml)	IL2 (IU/ml)	sIL-2R (U/ml)
A	18	0	476.03 $\pm$ 96.87	10.50 $\pm$ 5.18	20.89 $\pm$ 13.67	15.06 $\pm$ 5.74	24.11 $\pm$ 11.49	290.72 $\pm$ 187.73
B	17	2	605.14 $\pm$ 135.56	17.71 $\pm$ 10.88	31.41 $\pm$ 12.70	24.29 $\pm$ 7.70	13.78 $\pm$ 7.55	499.06 $\pm$ 296.70
C	7	6	865.82 $\pm$ 149.83	27.00 $\pm$ 8.21	75.29 $\pm$ 18.19	46.86 $\pm$ 11.39	9.42 $\pm$ 5.43	932.86 $\pm$ 476.94
F value			25.52	10.19	38.12	43.46	9.63	12.06
p value		0.001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001

Table 4. Comparison of the APACHE III Score and Levels of Cytokines between MODS and Non-MODS Groups

Group	n	APACHE III	IL6 (pg/ml)	IL8 (pg/ml)	TNF- α (pg/ml)	IL-1 β (pg/ml)	IL2 (IU/ml)	sIL-2R (U/ml)
MODS	8	96.4 $\pm$ 12.83	857.1 $\pm$ 149.10	24.8 $\pm$ 9.91	64.6 $\pm$ 28.01	41.5 $\pm$ 16.24	12.3 $\pm$ 8.32	899.5 $\pm$ 485.60
Non-MODS	34	58.3 $\pm$ 17.01	531.2 $\pm$ 124.84	14.2 $\pm$ 9.18	27.1 $\pm$ 15.81	20.0 $\pm$ 8.78	19.4 $\pm$ 9.85	383.9 $\pm$ 251.44
T value		5.922	6.410	2.898	3.659	3.622	-2.122	2.913
p value		0.0001	0.0001	0.006	0.006	0.007	0.04	0.02

Table 5. Comparison of APACHE III Score of SIRS Patients with or without MODS Following OPCAB and CCABG

	n	APACHE III score
CCABG	20	
MODS	6	101.67 $\pm$ 9.67
Non-MODS	14	62.78 $\pm$ 11.79 [#]
OPCAB	22	
MODS	2	80.50 $\pm$ 3.54
Non-MODS	20	55.20 $\pm$ 19.55 [#]

[#]p<0.05 compared to MODS.

decreased. Spearman's rank correlation analysis showed that the APACHE III score and levels of IL6, IL8, TNF- α , IL-1 β , and sIL-2R had positive correlations, $r_1=0.773$ ($p<0.01$), $r_2=0.573$ ($p<0.01$), $r_3=0.732$ ($p<0.01$), $r_4=0.805$ ($p<0.01$), $r_5=0.623$ ($p<0.01$), respectively, and that the APACHE III score and level of IL2 had a negative correlation, $r_6=-0.462$ ($p<0.01$). Stepwise regression analysis showed that the levels of IL-1 β , IL6, IL8, and sIL-2R had a significant influence on the APACHE III score ($p=0.0001$, 0.0001 , 0.0118 , 0.0168). The regression equation was $y=14.8290+0.0337x_1+0.4478x_2+0.7301x_4+0.0123x_6$ (y : APACHE III; x_1 : IL6; x_2 : IL8; x_4 : IL-1 β ; x_6 : sIL-2R).

A comparison of the APACHE III score and levels of cytokines between the MODS group and non-MODS group is shown in Tables 4 and 5. The APACHE III score of patients with MODS following CABG was significantly higher than those without MODS. It was also observed that the APACHE III score was significantly higher in the MODS group than in the non-MODS group following CCABG and OPCAB, respectively. At the same time, the levels of IL6, IL8, TNF- α , IL-1 β , and sIL-2R were significantly higher in the MODS group than in the non-MODS group, but the level of IL2 was significantly lower in the MODS group.

DISCUSSION

SIRS is a state of consistent progression of systemic inflammatory responses caused by various inflammatory or non-inflammatory diseases,⁵ and remains one of the major causes of morbidity or mortality in patients admitted to the

ICU. Inflammation and infection, resulting in SIRS, continue to be major causes of organ dysfunction and organ failure,⁶ with high mortality rates (ranging from 30 to 80%, depending on the seriousness and number of failing organs). The conception of SIRS is of great benefit to clinicians and researchers for dealing with systemic inflammatory responses and its sequelae.

However, we cannot diagnose the severity of a patient's condition and predict the probability of death depending solely on the criteria of SIRS. Therefore, new methods for its diagnosis are needed. The APACHE III scoring system is probably the most widely used critical care scale. The APACHE III scoring system has been recently introduced to estimate objectively patient risk on a daily base for mortality and other important outcomes. Some specialists³ take 60 for the demarcation score in the APACHE III scoring system. Researchers have found that the mortality rate is significantly different between an APACHE III score <60 and a score >60, and the higher the score is, the more serious the illness and the higher the mortality. Our research also shows that if the APACHE III score is <60, there is no MODS; if >60, the rate of MODS increases with the score, which means that the degree of SIRS also increases (as shown in Table 3). Meanwhile, the APACHE III score of patients with MODS following CABG, CCABG, or OPCAB is significantly higher than those without MODS, respectively (as shown in Tables 4 and 5). Therefore, the APACHE III score may be useful to some extent to judge the degree of SIRS following CABG.

It has been proved that the central link of SIRS is inflammatory cytokines. Inflammation in cardiac surgical patients is produced by complex humoral and cellular interactions with numerous pathways including activation, generation, or expression of thrombin, complement, cytokines, neutrophils, adhesion molecules, mast cells, and multiple inflammatory mediators.⁷ Because of the redundancy of the inflammatory cascades, profound amplification occurs to produce multi-organ system dysfunction that can manifest as coagulopathy, respiratory failure, myocardial dysfunction, renal insufficiency, and neurocognitive defects. However, absolute serum concentrations of cytokines involved in the pathophysiology of SIRS are normally not a reliable indicator of the severity

of the SIRS state and also do not allow prediction of the clinical outcome. The major pro-inflammatory cytokines involved are IL6, IL8, and TNF- α .^{8,9)} Researchers have proved that IL6 is responsible for induction of the synthesis of acute phase proteins and is the most important endogenous substance involved in inflammatory reactions and cytotoxicity. Its continuous elevation has a close relation with cardiac dysfunction following surgery. As a strong chemotactic factor, the serum level of IL8, whose elevation mostly occurs in the early stage of reaction, is correlated with the degree of myocardial ischemia. TNF- α , as the initial subject of inflammatory reaction, is the most potent inflammatory factor and provokes the cascade at the cellular and subcellular levels. It induces inflammatory factors such as IL-1 β and IL6, activates inflammatory cells, increases adhesion molecules, NO and oxygen free radicals, which further contribute to tissue destruction and results in MODS. The biological activity of IL-1 β is similar to that of TNF- α . Most research has showed that both TNF- α and IL-1 β can induce SIRS or MODS, and their levels in blood have good correlation with a severe degree of MODS.^{10,11)} IL-2 plays an important role in immune defense. It can combine with the membrane IL-2 receptor and then stimulates the maturity of T cells, enhances the function of natural killer cells and accelerates the secretion of immunoglobulins. Some authors¹²⁾ have found that soluble IL-2 receptors can competitively combine with IL2, resulting in the formation of an immunosuppressive complex and a decrease in the function of IL2. Although the mechanism and clinical significance of the elevation of sIL-2R levels after cardiac surgery is not clear, the decrease in IL2 and increase in sIL-2R are harmful for the immune defense system. We investigated the relationship between cytokine levels in SIRS cases and severity of SIRS. Our findings indicate that the severity of SIRS is related to the degree of inflammatory response. Patients in our study who developed MODS had higher plasma levels of IL-6, IL-8, TNF- α , IL-1 β , and sIL-2R and lower plasma level of IL-2. At the same time, the data suggest that the APACHE III score, plasma levels of IL6, IL8, TNF- α , IL-1 β , and sIL-2R, and morbidity of MODS increase gradually, while on the contrary, the level of IL2 decreases. As mentioned above, plasma levels of IL6, IL8, TNF- α , and IL-1 β in blood are closely correlated to the severity of illness, and the decrease in IL2 and increase in sIL-2R are harmful for the immune defense system. These findings indicate that the more serious the illness is, the higher the plasma levels of IL-6, IL-8, TNF- α , IL-1 β , and sIL-2R are and the lower the plasma level of IL-2. We also analysed the relationship between the plasma levels of cytokines and the APACHE III score of the cases with SIRS following CABG. Data suggest that the APACHE III score correlates positively with the values of IL-1 β , IL6, IL8, and sIL-2R, and correlates negatively with IL2. Only IL-1 β , IL6, IL8 and sIL-2R values have significant influences on the APACHE III score. Therefore, in addition to the APACHE III score, plasma IL-1 β , IL6, IL8 and sIL-2R levels may be effective predictors of the severity of SIRS, and routine measurements of plasma IL-1 β , IL6, IL8 and sIL-2R concentrations might be helpful to improve the prediction of mortality risk in patients with SIRS following CABG.

The APACHE III scoring system, which generates a point score based on 17 physiologic variables, age, and previous

health status, has been successfully used in the assessment of patients admitted to an intensive care unit. In our study, the APACHE III score might be used to some extent to judge the degree of SIRS following CABG. However, the APACHE III scoring system excludes parameters of immunologic function and inflammation reaction state so it is deficient in terms of evaluating these in patients. Furthermore, the APACHE III score can be used to assess the severity of the conditions of a group of patients instead of individuals.³⁾ Therefore, other methods should be complemented the APACHE III score to comprehensively assess the severity of SIRS. Inflammatory cytokines such as IL-1 β , IL6, IL8 and sIL-2R, whose levels reflect the individual inflammation reaction state or individual immunologic state, might be effective predictors of the severity of SIRS through our study. Now that both the APACHE III score and plasma levels of IL-1 β , IL6, IL8 and sIL-2R are correlative and may to some extent reflect the severity of SIRS following CABG (the former reflects the severity of the condition of a group of patients and the latter individual inflammation reaction state or individual immune state), synchronous measurements of the APACHE III score and plasma IL-1 β , IL6, IL8 and sIL-2R concentrations might be helpful to judge comprehensively the severity of SIRS following CABG, which would assist us in creating a new theory and a search for effective methods and drugs to interrupt the cascade of these cytokines at an appropriate point in time so as to improve a patient's condition and prognosis.

The results of the present study also indicate that SIRS after CCABG is more severe than that after OPCAB, which is reflected in the APACHE III score (Table 2), MODS score, assist ventilation time, and fever time (Table 1). The frequency of SIRS and morbidity of MODS were higher in the CCABG group than in the OPCAB group, although the differences between the two groups were not statistically significant. The differences were most likely due to the small sample size. Meanwhile, coronary revascularization with CPB was associated with a significant expression increase in IL6, TNF- α , IL-1 β and sIL-2R as well as a decrease in IL2 compared with the OPCAB patients (Table 2). Although IL-8 expression was slightly higher in OPCAB, the difference between the two groups was not statistically significant. We believe this may be related to the prolonged myocardial ischemia time due to temporary occlusion of the target coronary arteries in OPCAB. The data obtained in the present study indicate that, despite comparable surgical trauma, the OPCAB revascularization procedure without the use of CPB and cardioplegic arrest significantly alleviates systemic inflammatory response syndrome. This may contribute to improved organ function, subsequently resulting in improved postoperative recovery from surgical revascularization procedures, particularly in critically ill patients.

CONCLUSIONS

It is concluded that despite comparable surgical trauma, CPB is considered to be one of the most important factors in order to stimulate an inflammatory response. SIRS after OPCAB was clearly mitigated compared with CCABG. Determination of the APACHE III score and plasma IL-1 β , IL6, IL8 and sIL-2R concentrations might be helpful for evaluating the severity of SIRS following CABG and making a

prognosis.

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