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C-Reactive Protein and Complements as an Acute Phase Response after Cardiac Surgery

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Abstract:

Background: *A general activation of the immune system is observed during any operative procedure as a physiological response to the surgical trauma. Cardiopulmonary bypass may directly activate the inflammatory response by three distinct mechanisms: direct contact activation of the immune system following exposure of blood to the foreign surfaces, ischaemia-repurfusion injury to vital organs as a result of aortic cross clamping and splanchnic hypoperfusion can result in increased permeability of the gut mucosal barrier and consequently endotoxaemia.*

Objectives: *To observe the acute phase response (eg. increase C-reactive protein, complement C3 and C4) occurred postoperatively in patients underwent on-pump cardiac surgery.*

Methods: *This cross-sectional study was conducted in the Department of Cardiac Surgery, BSMMU from January 2009 to December 2010. Fifty patients were selected for the study and were divided into 2 groups on the basis of cardiopulmonary bypass time. Group I was cardiopulmonary bypass time less than 90 minutes and Group II was more than 90 minutes. P < 0.05 was considered statistically significant.*

Results: *The mean duration of cardiopulmonary bypass (CPB) time (55.76±10.8 in group I, 131±31.35 in group II; P<0.001) and Aortic cross clamp time (28.48±8.31 in group I, 83.48±30.99 in group II; P<0.001) was higher in group II than group I. CRP was significantly increased on 1st POD (P < 0.001) and on 5th POD it decreased significantly (P<0.001). Complement C3 and C4 both increased in 5th POD significantly P<0.001 and P<0.02 respectively. Analysis of outcome variables showed that mean postoperative ventilation time was 6.24±1.20 in group I and 9.16±2.33 in group II. There was significant difference in the ventilation time between two groups (P<0.001). This study showed that there is a definite relationship of wound infection with the prolonged cardiopulmonary bypass time (P<0.001) and increased acute phase response and also persistently rising CRP increases the chance of wound infection.*

Conclusion: *We may conclude that prolonged cardiopulmonary bypass time is associated with increased acute phase response and morbidity in cardiac surgical patients. CRP and Complement C3, C4 is easier and cheaper indicator of acute phase response in our context.*

Keywords: *Cardiopulmonary Bypass (CPB), Acute Phase Response, C-Reactive Protein (CRP), Complement C3 and C4, Wound Infection*

1. INTRODUCTION

A general activation of the immune system is observed during any operative procedure as a physiological response to the surgical trauma. Cardiopulmonary bypass may directly activate the inflammatory response by three distinct mechanisms: direct contact activation of the immune system following exposure of blood to the foreign surfaces, ischaemia-repurfusion injury to vital organs as a result of aortic cross clamping and splanhnic hypoperfusion can result in increased permeability of the

gut mucosal barrier and consequently endotoxaemia [1].The damaging effects of cardiopulmonary bypass (CPB) and the subsequent inflammatory response are the result of the extreme conditions encountered during extracorporeal support, including (1) cell activation on contact with the foreign surfaces of the bypass circuit, (2) mechanical shear stress, (3) tissue ischaemia and reperfusion, (4) hypotension, (5) nonpulsatile perfusion, (6) haemodilution with relative anaemia, (7) blood product administration, (8) heparin and protamine administration, and (9) hypothermia [2].Complement activation occurs through both the alternative (stimulated by foreign surface contact, endotoxin and kallikrein) and classical (protamine) pathways. The exposure of blood to extracorporeal circuits activates the alternate pathway, leading to the formation of C3a and C5a, whereas reversal of heparin with protamine activates the classical pathway with an associated rise in C4a levels and further rise in C3a levels [2,3]. One prominent initial physiological response to CPB is massive complement activation, primarily by the alternative pathway (Fig. 2). Plasma C3a levels increase within 2 minutes of CBP onset, remain elevated, and correlate with CPB duration. Removal of the cross-clamp and rewarming are characterized by an additional elevation of C3a levels, which peak at CPB termination five to 15-fold above baseline values. C3a levels return to normal 18 to 48 hours after surgery. Multiple organ dysfunction and overall morbidity have been strongly correlated with increased C3a levels following CPB [4].C-reactive protein is a typical marker of acute inflammation and bacterial infection. CRP is released from the liver and is involved in the acute inflammatory process [5]. The purpose of the study was to assess the acute phase response and morbidity of the patients after prolonged bypass surgery. It was expected that the study would help to diagnose the acute phase response in our perspective with available resources and forecast the complications beforehand so that appropriate measures could be taken accordingly.

1.1. Objectives

- To observe the acute phase response (eg. increase C-reactive protein, complement C3 and C4) occurred postoperatively in patients underwent on-pump cardiac surgery.

2. METHODS AND MATERIALS

This study was conducted in the Department of Cardiac Surgery, BSMMU from January 2009 to December 2010. Fifty patients were selected for the study and were divided into 2 groups on the basis of cardiopulmonary bypass time. Study design was Cross-Sectional and sampling technique was purposive. Fifty patients were selected for the study and were divided into two groups on the basis of cardiopulmonary bypass time. Group I was cardiopulmonary bypass time less than 90 minutes and Group II was more than 90 minutes. Follow up was taken up to 10^{th} postoperative day. After taking informed written consent blood samples were collected. With all aseptic precaution 10ml blood samples were collected in a plain test tube for the study of C-reactive protein and C3 and C4 on pre-operatively, 1^{st} postoperatively and 5^{th} postoperative day. C-reactive protein was measured by Immunonephelometric system (Cardio phase* *hs* CRP reagent code no. OQIY, Dade Behring, USA). C3c/ C4 by Immunonephelometric system (N antiserum to human C3c, code no. OSAP, N antiserum to human C4, code no. OSAO, Dade Behring, USA). Terumo Advanced Perfusion System 1, Heart-Lung Machine used for Cardiopulmonary Bypass and standard dose of heparin given before going to bypass. Also, standard dose of protamine given during withdrawal from bypass.This study has no potential risk to the patients and no experimental drug was used in this study. Before starting the study, ethical clearance was taken from the central ethical committee of BSMMU. Informed written consent was taken, all the procedures and benefits of this study was clearly explained to the patients. With all the aseptic precaution, blood collection done from the patient and it was ensured to them that there is no potential risk of this study.

3. RESULTS

In group- I, sixty-eight (68%) percent of the patients were in the range of 20-40 years. Twelve percent (12%) patients were in the range of less than 20 years; twenty percent (20%) patients are above 40 years. In Group- II, seventy-six percent (76%) patients were in the range of 20-40 years, eight percent (8%) patients were less than 20 years and sixteen percent (16%) patients were above 40 years. The patients in Group- II, had higher mean age 32.60 ± 14.85 years, compared to Group- I 27.40 ± 10.64 years. The difference between the two groups were statistically not significant (P = 0.162) (Table-I). Figure-I showed the sex distribution of the patients. Out of 50 patients, female was predominant 72%

in Group I, 60% in Group II. 28% of the patients in Group I and 40% in Group II were male. The two groups difference were not statistically significant (p = 0.37). Figure-II showed the types of operations that were done in two groups. The mean duration of cardiopulmonary bypass (CPB) time (55.76±10.8 in group I, 131±31.35 in group II; P<0.001) and Aortic cross clamp time (28.48±8.31 in group I, 83.48±30.99 in group II; P<0.001) was higher in group II than group I (Table-II). Table-III showed in each group, CRP was significantly increased on 1st POD (P < 0.001) and on 5th POD it decreased significantly (P<0.001). Complement C3 and C4 both increased in 5th POD significantly P<0.001and P<0.02 respectively. Analysis of outcome variables showed that mean postoperative ventilation time was 6.24±1.20 in group I and 9.16±2.33 in group II. There was significant difference in the ventilation time between two groups (P<0.001) (Table-IV). Again 5(20%) of the patients in group I developed Atrial fibrillation (AF) in the postoperative period, whereas 12(48%) of the patients in group II developed atrial fibrillation in postoperative period. The difference between both groups was statistically significant (P<0.05). Mean length of ICU stay was 5.04±0.20 days in group I and 5.76±1.45 in group II. The difference was significant (P<0.02). None of the patients developed severe systemic inflammatory response syndrome or acute renal failure or severe arrhythmia endangering the life. Only local wound infection occurred in 2(8%) in group I and 4(16%) in group II. The difference was significant (P<0.001). This study showed that there was a definite relationship of wound infection with the prolonged cardiopulmonary bypass time (P<0.001) and also persistently rising CRP increases the chance of wound infection (Table-V).

Table1. *Age distribution of the study (n=50) groups*

Age (years)	Group I (n=25)	Group II (n=25)	P value
< 20	3 (12%)	2 (8%)	0.162 NS
20-40	17 (68%)	19 (76%)	
> 40	5 (20%)	4 (16%)	
Mean ± SD	27.40 ± 10.64	32.60 ± 14.85	

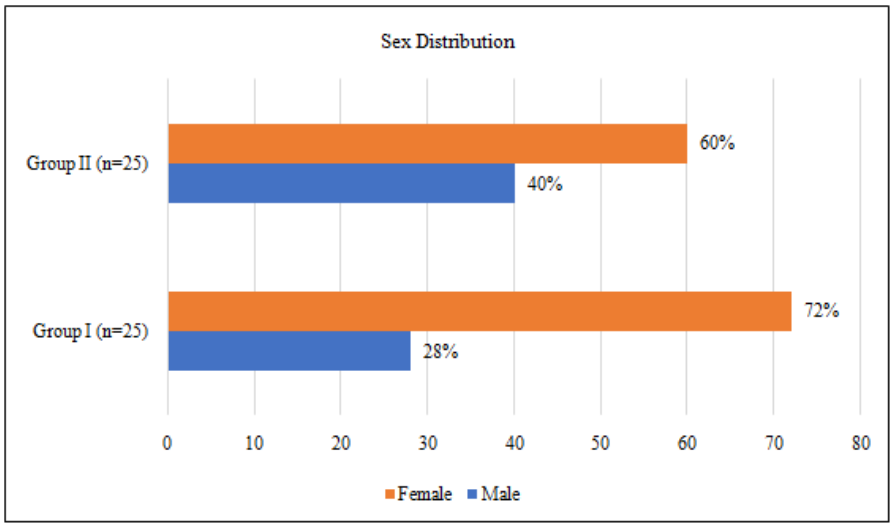

Figure1. *Bar diagram showing sex distribution of the patients*

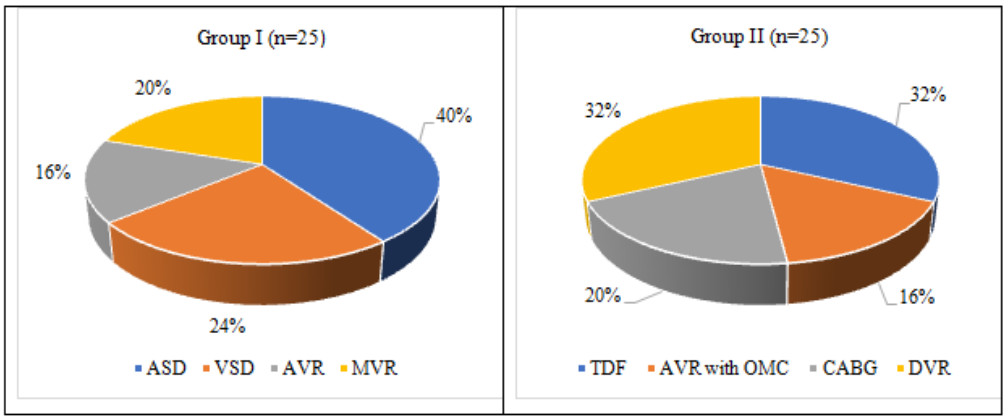

Figure2. *Pie chart showing percentage of different types of operation of the study population*

Table2. *Comparison of per-operative variables (n=50)*

Age (years)	Group I (n=25) (mean±SD)	Group II (n=25) (mean±SD)	P value
Cardiopulmonary Bypass Time	55.76±10.85	131±31.35	P<0.001 S
Aortic cross clamp time	28.48±8.31	83.48±30.99	P<0.001 S

Table3. *Variables of Group I and II at a glance*

Day	Group	CRP	C3	C4
Pre-operative day	Group I	0.94 ± 0.60	1.32 ± 0.20	0.27±0.11
	Group II	1.14 ±0.61	1.26 ±0.19	0.19±0.10
1st Postoperative	Group I	99.12±44.33	0.94 ± 0.17	0.21±0.05
	Group II	109.30±40.67	0.92 ± 0.18	0.17±0.06
5th Postoperative	Group I	71.35 ± 0.23	1.35 ± 0.23	0.27±0.05
	Group II	75.73 ± 67.04	1.35 ± 0.23	0.26±0.09
P value	Group I	P<0.001S	P<0.001S	P<0.02S
	Group II	P<0.001S	P<0.001S	P<0.01S

One-way ANOVA done, P ≤ 0.05 is significant, CRP = C-reactive protein, C3= Complement C3, C4= Complement C4.

Table4. *Comparison of postoperative events and complications between two groups*

Variable	Group I (n=25)	Group II (n=25)	P value
Postoperative ventilation time (Hours)#	6.24±1.20	9.16±2.339	P<0.001S
Postoperative ICU stay# (Days)	5.04±0.20	5.76±1.45	P<0.02 S
Postoperative AF*	5(20%)	12(48%)	P<0.05S
Wound infection*	2(8%)	4(16%)	P<0.001S

** Chi-square (x2) test done, # Student's t-test done, AF= Atrial fibrillation, N= no of patients, NS= Not significant, S= Significant Yate's correction done in Chi-square (x2) test of wound infection and the 'P' value is <0.001.*

Table5. *Distribution of wound infection among persistently raised CRP populations (n=7)*

Variable	n=7	%
Group I	1	14.29
Group II	6	85.71
Total no of persistently high CRP	7	100.0

4. DISCUSSION

The mean age of the patients were 27.40 ± 10.64 years in Group-I and 32.60±14.85 years in Group II (Table-I), although the mean age of Group-II was higher than that of Group- I. The difference was not statistically significant (P = 0.162). Comparison could not be done due to scarcity of the literature. Out of 50 patients, females were predominant in both Group I (72%) and Group II (60%). Only 7(28%) in Group and 10(40%) in Group II were male. The percentage difference between two groups was not statistically significant (P=0.370). Bruins and colleagues13 and Black and colleagues [6] found that the acute phase response was biochemically marked by the enhanced production of the prototypical acute phase protein CRP and by the levels of total C3 and C4 level. We had also studied the same variables. Our study showed raised CRP in 1st POD but C3 and C4 level declined from their baseline which was dissimilar with the previous study done by Bruins and colleagues [7]. Complement C3 and C4 declined from their baseline in our study was probably due to complement consumption. Bruins and colleagues showed that Total complement C3 and C4 raised after CPB, we also tried to study the Total Complement C3 and C4 but our reagent can only measure C3c component of complement C3 and C4a component of Complement C4 [7]. This was the cause of dissimilarity of the study done by Bruins and colleagues7. In the 5th postoperative day both the C3 and C4 again raised to their near normal level. But it never rose beyond the normal range which is contradictory to study done by Bruins and colleagues [7,8]. CRP mean value increased after cardiopulmonary bypass, from preoperative value 0.94 ± 0.60 to 99.12±44.33 on 1st postoperative day in group-I and 1.14 ±0.61 to 109.30±40.67 on 1st postoperative day in group-II. And decreased from 1st postoperative day value to 59.86±36.15 on 5th postoperative day in group-I and 75.73±67.04 on 5th postoperative day in group-II. This result was consistent with the study done by Rothenburger and colleagues [5].

The mean duration of cardiopulmonary bypass (CPB) time (55.76±10.85 in group I, 131±31.35 in group II; P<0.001) and Aortic cross clamp time (28.48±8.31 in group I, 83.48±30.99 in group II; P<0.001) was higher in group- II than group- I. The difference between the groups was statistically significant. Analysis of outcome variables showed that mean postoperative ventilation time was 6.24±1.20 in group I and 9.16±2.33 in group II (Table-IV). There was significant difference in the ventilation time between two groups (P<0.001). Five (20%) of the patients in group I developed Atrial fibrillation (AF) in the postoperative period, whereas twelve (48%) of the patients in group II developed atrial fibrillation in postoperative period (Table-III). The difference between both groups was statistically significant (P<0.05). Mean length of ICU stay was 5.04±0.20 days in group I and 5.76±1.45 in group II (Table-IV). The difference was significant (P<0.02). This result is consistent with Cappabianca and colleagues 9,10. This study showed that there is a definite relationship of wound infection with the prolonged cardiopulmonary bypass time (P<0.001) and also persistently rising CRP increases the chance of woundinfection which was consistent with the study done by Rothenburger and colleagues, Wesselink and colleagues, Kumle and colleagues, Cole and colleagues [5,11,12,13].None of the patients developed severe systemic inflammatory response syndrome or acute renal failure or severe arrhythmia endangering the life. This result is consistent with Cosgrave and colleagues [10].

5. CONCLUSION

From this study, we may conclude that prolonged cardiopulmonary bypass time is associated with increased acute phase response and morbidity in cardiac surgical patients.

RECOMMENDATION

C-reactive protein andComplement C3, C4 can predict the acute phase responsein on-pump cardiac surgical patients. So, it should be checked up to 7th postoperative day.

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