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Increased preoperative C-reactive protein (CRP)-values without signs of an infection and complicated course after cardiopulmonary bypass (CPB) – operations[1]

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Abstract

Objective: C-Reactive protein (CRP) is known to be a sensitive indicator of infection. Since it is also involved in the acute phase reaction, it is of great interest, whether an isolated preoperative increase of CRP without further signs of infection is of any prognostic value for postoperative outcome after cardiac surgery with cardiopulmonary bypass (CPB), which itself is possibly causing a systemic inflammatory response syndrome (SIRS). **Methods**: Fifty patients with an isolated CRP-elevation (>5 mg/l) (from 6.2 to 93.3 mg/l) were operated using CPB (group A). A control group (group B) consisted of 50 cardiac surgery patients, matched in the patterns of age, gender and kind of disease. No preoperative CRP-elevation (from 0 to 4.8 mg/l) occurred in this group. **Results**: The postoperative course of both groups showed significant differences. Septic complications were seen more often in group A (20%) than in the controls (2%) ($P < 0.01$). Microbiology (blood culture, cultures from nose, tracheal aspirate and urine) was positive only in 10% of these patients. Catecholamine support (epinephrine, norepinephrine and/or doses of dopamine or dobutamine of more than 3 μg/kg per min) was needed in 26% of group A cases, whereas it was only needed in 10% of group B ($P < 0.05$). A significantly longer respiratory support was also necessary in patients with elevated CRP (25.2 ± 6.4 h vs. 6.6 ± 0.8 h) ($P < 0.01$). Furthermore there was a significant difference in the duration of intensive care (4.6 ± 0.8 days vs. 2.6 ± 0.3 days) ($P < 0.05$). **Conclusions**: These data show that patients without apparent infection or inflammation, who had elevated CRP-values preoperatively, face an increased risk of septic complications after extracorporeal circulation. As microbiology tests are negative in most cases, it may be speculated that the majority of septic complications are due to a SIRS.

Keywords: C-Reactive protein; Postoperative complications; Systemic inflammatory response syndrome; Sepsis; Cardiopulmonary bypass

1. Introduction

The C-reactive protein (CRP)-value is a sensitive indicator for an infection [1]. The discovery of this protein in 1930 led to the description of the acute-phase reaction which is a fundamental response of the body to injury [2]. It is now recognized as a general and non-specific response to most forms of infective and non-infective inflammatory processes, cellular and tissue necrosis, and malignant neoplasia. The rate of CRP-synthesis and secretion increases within hours after an acute injury or the onset of inflammation. The median value in healthy adults is normally less than 3 mg/l, it may reach peak levels of as much as 300 mg/l within 24–48 h [3].

CRP provides useful information in patients with ischemic conditions, especially myocardial infarction; there is an excellent correlation between the peak levels of CRP and of creatine phosphokinase MB [4–8]. The CRP-value also rises after major surgery, cardiopulmonary bypass (CPB) or in case of a systemic inflammatory response syndrome (SIRS) [9–12]. Kirklin already hypothesized that the deleterious effects of CPB were secondary

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to the exposure of blood to abnormal surfaces in the bypass circuit, which initiated a 'whole body inflammatory response'. He noted that this response is characterized by activation of coagulation, the kallikrein system, fibrinolysis, and complement, all of which are now recognized as the mediators of the disseminated intravascular post-pump syndrome [13,14].

In cardiac surgery there are patients with an isolated preoperative CRP-elevation without further signs of infection. They are clinically inapparent and all other parameters like leukocytes and erythrocytes sedimentation rate (ESR) are normal. In most cases CRP-elevation can not be explained by myocardial ischaemia or even infarction. The reason for this elevation is often not clear. In many cases it is not possible to wait with the operation until the CRP-value has normalized again.

This paper describes the correlation between this CRP-elevation and complications after extracorporeal circulation, especially the development of a systemic inflammatory reaction.

2. Patients and methods

To evaluate the correlation between preoperative CRP-elevation and postoperative complications we retrospectively compared two groups of patients without apparent infection or inflammation undergoing CPB. The CRP-values were measured by nephelometry (Nephelometer 100, Behring, Frankfurt, Germany) and the detection limit was 0.3 mg/l. None of these patients suffered from ongoing myocardial ischemia or fresh infarction. All patients were operated on the basis of elective indication for surgery. Both groups were matched in the patterns of age, gender, left ventricular function and kind of operation. We included both, coronary artery bypass grafting (CABG) and combined procedures, that means CABG and valve-surgery.

The CPB technique and the anesthetic management were identical for all procedures. Cardioplegia was induced by an intraaortic infusion of 4°C cold Bretschneider solution. All patients were given prophylactic antibiotics with cefazolin during the operation and through the following day. There was no significant difference in the mean perfusion time and in the duration of ischemia in both groups.

Table 1

Demographic and clinical data of the patients with elevated and normal preoperative CRP-values

	(CRP > 5 mg/l) Group A	Group B
n	50	50
Gender (M/F)	30:20	33:17
CRP (mg/l)	24 ± 4	0.4 ± 0.1*
Ejection fraction (%)	64.3 ± 5.2	65.1 ± 6.1
CABG	30	33
CABG + valve	20	17
CPB (min)	120 ± 34	127 ± 37
Duration of ischemia (min)	62 ± 22	69 ± 15

*$P < 0.05$.

Table 2

Definition of septic complications after cardiopulmonary bypass (according to Ref. [22])

Defined by at least two of the following clinical conditions	
Body temperature	>38°C or <36°C
Heart rate	>90 beats/min
Respiratory rate	>20 breaths/min
pCO_2	<32 mmHg
White blood cell count	>12000/μl or<4000/μl
Immature forms	>10% of neutrophils

Group A consisted of 50 cardiac surgery patients with an isolated CRP-elevation (>5 mg/l), the mean value was 24 mg/l (range: 6.2–93.3 mg /l). All patients in group A did not have clinical signs of an infection, all other parameters like leukocytes and ESR were normal, and a rheumatic disease or a malignant neoplasia was excluded.

No preoperative CRP-elevation occurred in the control group B, the mean value was 0.4 mg/l (range: 0–4.8 mg/l) (Table 1).

The time points for the preoperative CRP-measurement were 1.5 ± 0.6 days before operation in group A and 2.2 ± 1.2 days in the control group.

All data were compared by *t*-test respectively χ^2-test and $P < 0.05$ was regarded as significant. In all cases we used the standard error of the mean (SEM).

Postoperative septic complications were defined as at least two of the clinical conditions shown in Table 2.

3. Results

The postoperative course of both groups showed significant differences:

Septic complications as defined in Table 2 were seen in 20% ($n = 10$) of the patients with preoperatively elevated CRP-levels and only in 2% of group B. Septic complications include a hyperdynamic circulatory state with an increased cardiac index (CI) and a reduced systemic vascular resistance (SVR) combined with a higher need for volume. In only one of these patients it was possible to get a positive microbiology (*Pseudomonas aeruginosa* in two blood cultures), in all other cases no reason for the syndrome of sepsis could be found.

In group A, a significant increase in CI was observed when septic complications began. This increase was significantly different from values in control patients at the same time point (group A: $5.3 \pm 1.3\ l \times min^{-1} \times m^{-2}$, group B: $2.7 \pm 0.74\ l \times min^{-1} \times m^{-2}$) ($P < 0.05$). Concomitant with changes in CI, a significant decrease in SVR occurred in

Table 3
Postoperative course in both groups of patients

	(CRP5 mg/l)		
	Group A	Group B	*P*-value
Catecholamine support (%)	13 (26)	5 (10)	0.028
Respiratory support (h)	25.2 ± 6.4	6.6 ± 0.8	0.005
ICU-stay (days)	4.6 ± 0.8	2.6 ± 0.3	0.013
Septic complications (%)	10 (20)	1 (2)	0.005
→ positive microbiology	→ 1	→ 0	
Early mortality (hospital, %)	2 (4)	0	n.s.
Hospital stay (days)	17	15	n.s.
CRP (mg/l) (3rd day after operation)	36.2 ± 16.4	17.3 ± 10.3	0.03

n.s., not significant.

group A (group A: 605 ± 223 dyn × s × cm^{-5}, group B: 1128 ± 407 dyn × s × cm^{-5}) ($P < 0.05$).

Catecholamine support was necessary in 26% ($n = 13$) of group A cases, whereas it was only needed in 10% ($n = 5$) of group B. Catecholamine support was defined as the need for epinephrine or norepinephrine, and/or doses of dopamine or dobutamine of more than 3 μg/kg per min. Indications for inotropic support were a systolic blood pressure of less than 100 mmHg or a mean arterial pressure of less than 60 mmHg over a period of time of more than 10 min despite sufficient volume substitution.

Weaning from the respirator was significantly prolonged in the cases of preoperative CRP-elevation with 25.2 h vs. 6.6 h in the controls ($P < 0.05$). The respirator therapy was finished when the patients were breathing spontaneously and had sufficient arterial blood gases with $FiO_2 \leq 0.3$ without the need for mechanical assistance (CPAP/ASB < 5 cm H_2O).

Duration of intensive and/or intermediate care was also significantly longer in group A with 4.6 days compared to 2.6 days in group B ($P < 0.05$) (Table 3).

In contrast to that there was no significant difference in the duration of hospital stay in both groups. Two patients of group A died during the early postoperative course, one on day 2 (perioperative myocardial infarction), another patient on day 9 (intestinal ischemia), whereas there was no mortality in group B during the stay in hospital.

According to the differences in the clinical postoperative course between the two groups, we found in addition significantly different CRP-values on the 3rd day after the operation with 36.2 ± 16.4 mg/l in group A, compared to 17.3 ± 10.3 mg/l in the controls ($P < 0.05$).

4. Discussion

The measurement of CRP has been used for the early recognition of infection or inflammation. In connection with the search for potential risks of postoperative infections and endocarditis the CRP has been determined routinely in patients before cardiac valve surgery in our department. Analyzing patients with complicated postoperative courses after heart surgery, either valve surgery or coronary bypass surgery, we found more incidentally that many patients had a perceptible elevation of CRP-values preoperatively. We therefore made a retrospective study of one group of patients with elevated CRP-levels and another group of patients with preoperatively normal CRP-values. Consequently it was not possible to blind the clinical investigators for the study, the effect might have been a similar one, however.

In general, increased CRP production is a feature of non-infective as well as infective diseases, and CRP binds to a wide range of autogenous products (lipids and phospholipids, polycations and polyanions) all of which are constituents of cells and likely to be abnormally exposed in or released from damaged tissues. In-vivo binding of CRP to necrotic cells has been described and may contribute to resolution and repair. However, it is proposed that the main role of CRP is to recognize in plasma the potential toxic autogenous materials released from damaged tissues, to bind to them, and thereby to detoxify them and facilitate their clearance [1].

CRP-levels invariably rise after major surgery, but with an uncomplicated postoperative recovery they fall towards normal over a period of 7–10 days. Absence of this fall or a secondary rise in CRP provides early warning of intercurrent infection or of thrombembolic complications [1,2]

4.1. CRP in cardiac surgery/on intensive care unit

In cardiac surgery we can see an elevation of CRP in patients with unstable angina or even myocardial infarction, with the rise starting 20–40 h post infarction or ischemia. There is even a correlation between the levels of CRP and of creatine phosphokinase MB [5,6,9,10,15–19]. Patients with high serum CRP-levels might even have a high probability of occurrence of subacute cardiac rupture after acute myocardial infarction [20].

Several authors demonstrated the importance of the CRP as an indicator of resolution of sepsis in the intensive care unit [3].

Other authors did not find a statistical difference in the CRP-concentrations after CPB between patients suffering from complications and patients free of complications [21].

4.2. CRP and postoperative septic complications/SIRS

In the past the value of preoperatively elevated CRP-concentrations for predicting complications after cardiac surgery has been controversially discussed. There was no evidence of a correlation between a preoperative CRP-elevation in clinically inapparent patients and postoperative complications, especially septic complications after extracorporeal circulation. The data of our study show that these

inapparent patients with elevated CRP-levels face an increased risk of septic complications after extracorporeal circulation (ECC). In only one patient it was possible to get a positive microbiology according to an infective reason for the sepsis syndrome. All other, non-infective, cases might have been of the systemic inflammatory response type.

The pathophysiologic entity of a sepsis syndrome reflects a hyperdynamic circulatory state including an increased cardiac output in the presence of reduced systemic vascular resistance [22]. This requires the treatment by vasoconstrictive agents like norepinephrine or even epinephrine in the septic patients.

The prolonged weaning from the respirator in these patients seems to be the consequence of the impaired pulmonary function in the conditions of sepsis.

Because of the complicated postoperative course of patients with elevated CRP-levels, we believe that these patients should not be operated on using CPB unless there is an urgent indication. In the future it must be shown whether there is a correlation between quantitative measurement of preoperative CRP and the risk of postoperative septic complications. It would be of interest to investigate the effect of a presurgical antibiotic treatment on the postoperative outcome of these patients.

As microbiological tests, like cultures from blood, nose, tracheal aspirate and urine, were negative in most of our patients, we rather suppose that the sepsis was of the systemic inflammatory response type. In further studies we have to evaluate the release of certain mediators after CPB, like CRP, interleukin-6 and procalcitonin. Cremer et al. described significantly higher serum-levels of IL-6 in patients with a SIRS [23]. To distinguish between a SIRS and an infection, procalcitonin could be useful, as it only seems to be elevated in infective conditions and not in SIRS patients [11,24].

Taylor suggests that a SIRS is induced in all patients after cardiac operation, but the severity is variable. Only 10% of these patients suffer from hemodynamic disturbance [22]. So the preoperative CRP-value may be a potential indicator to select these patients.

On the grounds of the results in this retrospective analysis of patients undergoing cardiac surgery we can draw the following conclusions.

5. Conclusions

- CRP seems to be a sensitive indicator to select the patients who may suffer from postoperative complications after extracorporeal circulation.
- Patients with high CRP-levels should not be operated upon using CPB unless it is an emergency situation.
- As microbiology tests are negative in most cases, it may be speculated that the majority of septic complications after ECC is due to a SIRS.

References

[1] Pepys MB. C-Reactive protein fifty years on. Lancet 1981;21:653–656.
[2] Thompson D, Milford-Ward A, Whicher JT. The value of acute phase protein measurements in clinical practice. Ann Clin Biochem 1992;29:123–131.
[3] Yentis SM, Soni M, Sheldon J. C-Reactive protein as an indicator of resolution of sepsis in the intensive care unit. Intensive Care Med 1995;21:602–605.
[4] Liuzzo G, Biasucci L, Gallimore R, Grillo RL, Rebuzzi AG, Pepys MB, Maseri A. The prognostic value of C-reactive protein and serum amyloid A protein in severe unstable angina. N Engl J Med 1994; 331:417–424.
[5] Ikeda U, Ohkawa F, Seino Y, Yamamoto K, Hidaka Y, Kasahara T, Kawai T, Shimada K. Serum interleukin 6 levels become elevated in acute myocardial infarction. J Mol Cell Cardiol 1992;24:579–584.
[6] Pietila K, Harmoinen A, Hermens W, Simoons L, van de Werf F, Verstraete M. Serum C-reactive protein and infarct size in myocardial infarct patients with a closed versus an open infarct-related coronary artery after thrombolytic therapy. Eur Heart J 1993;14:915–919.
[7] Haverkate F, Thompson SG, Duckert F. Haemostasis factors in angina pectoris; relation to gender, age and acute-phase reaction. Thromb Haemost 1995;73:561–567.
[8] Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Am J Epidemiol 1996;144:537–547.
[9] Aronen M. Value of C-reactive protein in detecting complications after closed-heart surgery in children. Scand J Thorac Cardiovasc Surg 1990;24:147–151.
[10] Aronen M. Value of C-reactive protein in detecting complications after open-heart surgery in children. Scand J Thorac Cardiovasc Surg 1990;24:141–145.
[11] Seghaye MC, Duchateau J, Grabitz RG, Faymonville FL, Messmer BJ, Buro-Rathsmann K, von Bernuth G. Complement activation during cardiopulmonary bypass in infants and children. J Thorac Cardiovasc Surg 1993;106:978–987.
[12] Mbewu AD, Durrington PN, Bulleid S, Mackness MI. The immediate effect of streptokinase on serum lipoprotein(a) concentration and the effect of myocardial infarction on serum lipoprotein(a), apolipoproteins A1 and B, lipids and C-reactive protein. Atherosclerosis 1993;103:65–71.
[13] Salgado A, Boveda JL, Monasterio J, Segura RM, Mourelle M, Gomez J, Peracaula R. Inflammatory mediators and their influence on hemostasis. Haemostasis 1994;24:132–138.
[14] Boyle EM, Pohlman TH, Johnson MC, Verrier ED. Endothelial cell injury in cardiovascular surgery: the systemic inflammatory response. Ann Thorac Surg 1997;63:277–284.
[15] Heinrich J, Schulte H, Schönfeld R, Köhler E, Assmann G. Association of variables of coagulation, fibrinolysis and acute-phase with atherosclerosis in coronary and peripheral arteries and those arteries supplying the brain. Thromb Haemost 1995;73:374–379.
[16] Thompson SG, Kienast J, Pyke SD, Haverkate F, van de Loo JCW. Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. N Engl J Med 1995;332:635–641.
[17] Kazmierczak M, Sobieska M, Wiktorowicz K, Wysocki H. Changes of acute phase proteins glycosylation profile as a possible prognostic marker in myocardial infarction. Int J Cardiol 1995;49:201–207.
[18] Bolo-deoku J, Wilcox AH, Barron JL. The use of C-reactive protein in the evaluation of, chest pain of cardiac origin. Ann Clin Biochem 1992;29:465–466.
[19] Butler J, Pathi VI, Paton RD, Logan RW, MacArthur KJ, Jamieson

MP, Pollock JC. Acute-phase responses to cardiopulmonary bypass on children weighing less than 10 kilograms. Ann Thorac Surg 1996; 62:538–542.
[20] Ueda S, Ikeda U, Yamamoto K, Takahashi M, Nishinaga M, Nago N, Shimada K. C-Reactive protein as a predictor of cardiac rupture after acute myocardial infarction. Am Heart J 1996;31:857–860.
[21] Aronen M, Leijala M, Meri S. Value of C-reactive protein in reflecting the magnitude of complement activation in children undergoing open heart surgery. Intensive Care Med 1990;6:28–132.
[22] Taylor KM. SIRS – the systemic inflammatory response syndrome after cardiac operations. Ann Thorac Surg 1996;61:1607–1608.
[23] Cremer J, Martin M, Redl H, Bahrami S, Abraham C, Graeter T, Haverich A, Schlag G, Borst HG. Systemic inflammatory response syndrome after cardiac operations. Ann Thorac Surg 1996;61:1714–1720.
[24] Biasucci LM, Vitelli A, Liuzzo G, Altamura S, Caligiuri G, Monaco C, Rebuzzi AG, Ciliberto G, Maseri A. Elevated levels of interleukin-6 in unstable angina. Circulation 1996;94:874–877.

Appendix A. Conference discussion

Dr P. Sergeant (*Leuven, Belgium*): Was the CRP-value known to the attending physicians at the time of treating their patients! You might be overtreating a patient, knowing that the CRP-value was elevated, be more influenced by the CRP-value than the actual clinical setting of the patient. Can you comment on that?

Dr Feindt: In most cases they know.

Dr Sergeant: It was known?

Dr Feindt: Even if they know no special therapy was given, because no source of elevated CRP-levels was found in these patients.

Dr B. Walpoth (*Bern, Switzerland*): Did you look into the time course of CRP of those two groups and could you comment on it? And did you look at other more specific mediators of SIRS to back up you findings?

Dr Feindt: As I mentioned at the end of my presentation this has to be clarified in a prospective study. In this presented retrospective study only the clinical signs of SIRS can be looked at. To your second question: we have not measured mediators of SIRS.

Dr Walpoth: Regarding the time course after surgery, did those patients who had elevated CRP before surgery have a much longer and higher elevation of CRP?

Dr Feindt: Yes.

Dr Walpoth: So there is a correlation?

Dr Feindt: Yes.

Dr Walpoth: Is there a correlation from before to after surgery?

Dr Feindt: There is a correlation between the CRP-value and the clinical condition of SIRS with a longer elevation of CRP-levels after surgery.

Dr R. Bauernschmitt (*Heidelberg, Germany*): Could you comment on the cardiac situation of your patients prior to surgery. Because there is some evidence that chronic heart failure, congestive heart failure, may increase some mediators of the acute phase response and make the patients perhaps more vulnerable to the damaging effects of cardiopulmonary bypass.

Dr Feindt: That's right. But these two groups are matched only concerning the difference of CRP-levels. All the other factors are the same in both groups. Emergency situations, myocardial infarction, etc. were exclusion criteria for this study.

Dr W. Dimitri (*Coventry, UK*): You mentioned in your conclusion that they shouldn't be operated on without urgent indications. You're going to look at the effect of antibiotics. But if you waited, would the CRP-levels come down to normal? And how long would you have to wait?

Dr Feindt: That is difficult to answer. Our conclusion was: when the CRP-level is above 5 mg/l, we wait. Very often after 1 week, the CRP-values are normal again when there is no clinical sign for another infection. The other conclusion we draw from these results: we check that for every patient before cardiac surgery.