

C-Reactive Protein Kinetics after Cardiac Surgery: A Retrospective Multicenter Study

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ABSTRACT

Background: Recognition of postoperative infection after cardiac surgery is challenging. Biomarkers may be very useful to recognize infection at early stage, but the literature is controversial.

Methods: We conducted a retrospective study at two large University Hospitals, including adult patients undergoing cardiac surgery (excluding those with preoperative infections, cirrhotic or immunocompromised). We evaluated the kinetics of C-Reactive Protein (CRP) and White Cell Count (WCC) during the first postoperative week. Primary outcomes were CRP and WCC changes according to the development of postoperative infection. In order to evaluate the influence of cardiopulmonary bypass on biomarker kinetics, we also studied CRP and WCC changes in patients without postoperative infection and undergoing on- vs off-pump coronary-artery bypass grafting.

Results: Among 429 included, 45 patients (10.5%) had evidence of postoperative infection. Patients with postoperative infection had higher CRP and WCC values than those without infection, with between-groups difference becoming significant from postoperative day 2 for CRP (120.6 ± 3.6 vs. 134.6 ± 7.9 , $P < 0.01$), and from postoperative day 3 for WCC (10.5 ± 0.5 vs. 9.9 ± 0.2 , $P = 0.02$). Over the postoperative period, CRP and WCC showed significant within-group changes regardless of development of postoperative infection ($P < 0.001$ for both). We found no differences in CRP and WCC kinetics between patients undergoing on- vs off-pump procedure.

Conclusions: During the first week after cardiac surgery, CRP increases one day earlier than WCC in patients developing postoperative infections, with such difference becoming significant on the second postoperative day. In not infected patients, use of cardiopulmonary bypass does not influence CRP and WCC kinetics.

Keywords: Biomarkers, cardiac surgery, infection

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INTRODUCTION

Identification of postoperative infection is challenging after surgery. The pathophysiological inflammatory response occurring preoperatively can hide the host response to infection, thus delaying diagnosis of postoperative infection.

Whilst the development of postoperative fever is common and by itself should not trigger antibiotics prescription,^[1] the use of traditional biomarkers such as White Blood Cells (WCC) alone is clearly insufficient to prove infection.^[2] In addition to clinical signs, other biomarkers such as

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C-Reactive Protein (CRP) or procalcitonin (PCT) may be helpful in identifying a postoperative infection.^[3,4] Among the latter, CRP is almost routinely measured^[5] and it is much less expensive than PCT. It has already been shown that CRP levels increase after major surgery (neurosurgery and abdominal surgery), but to a much larger extent in those developing postoperative infection.^[6] However, the diagnosis of perioperative infection is very challenging after cardiac surgery where the inflammatory response can also be influenced by the use of cardiopulmonary bypass (CPB) and extracorporeal circulation;^[7] moreover, considering the significant comorbidities of patients undergoing cardiac surgery, many of them may experience hypotension and/or tachycardia for non-infective reasons.^[8] Therefore, although an increase in pro-inflammatory cytokines has been associated with an unfavorable outcome, the results available in the literature regarding cardiac surgery are still controversial.^[9,10]

The objectives of this multicenter retrospective study were to analyse the CRP and WCC kinetics during the first postoperative week after cardiac surgery, separating patients according to development of postoperative infection. We also investigated the influence of CPB on the inflammatory response as described by CRP and WCC kinetics.

Methods

This is a two-center observational retrospective study conducted over a 10-month period. We included all adult (>18 years) patients undergoing cardiac surgery in two Departments: The Cardio-Thoracic Critical Care Unit (18 beds) at John Radcliffe Hospital in Oxford (Institution A), and the Department of Intensive Care (34 beds) at Erasme University Hospital in Brussels (Institution B). Institution A accepted the role of Research Sponsor for this study (Research and Development Reference: 10725). As routine clinical practice in one institution (Institution B) a bolus of intravenous 500 mg of methylprednisolone was administered before institution of CPB.

Data were collected anonymously and participants were assigned a study number. Due to the retrospective nature of data collected, the Ethical Committee waived the need for ethical consent.

Inclusion and exclusion criteria

We included all adult patients undergoing cardiac surgery with median sternotomy and conducted on- or off-CPB. Exclusion criteria were: Surgery of the aorta; ongoing preoperative infections (including endocarditis), other thoracic interventions, trauma, pregnancy, immune-compromised patients or those with cirrhosis.

Data collection

A part from demographics, EUROSCORE and sequential organ failure assessment (SOFA) score on ICU admission, we daily collected the following data during the first postoperative week: Clinical and microbiological data, CRP and WCC values, antibiotic therapies.

In Institution A, the serum CRP concentration was measured using a laser nephelometric technique (*BN 100, Medgenix Diagnostics*). In Institution B, CRP was measured by immunoturbidimetric assay (*Roche on Cobas 8000*); standard methods were used to measure the other variables.

Group stratification and outcomes

As primary outcomes, we evaluated the differences in both CRP and WCC kinetics during the first postoperative week in the whole population of patients undergoing cardiac surgery. We separated these patients according to the development or not of postoperative infection, which was defined as per International Sepsis Forum Consensus Conference on Definitions of Infection in Intensive Care Unit (ICU).^[2]

Subsequently, we performed also sub-group analyses in which the primary outcomes were investigated according to the type of surgery performed. Therefore we analyzed 4 sub-groups: 1) on-CPB coronary artery bypass grafting (on-CABG); 2) off-CPB CABG; 3) valvular surgery (with valve replacement - R, or repair - r); 4) on-CABG + valvular surgery.

As secondary endpoint we tried to investigate the effects of CPB on both CRP and WCC kinetics. Thus, these outcomes were assessed in patients undergoing isolated CABG and not developing postoperative infection, separating them in procedures performed on- and off-CPB.

Statistical analysis

Statistical analyses were performed using IBM® SPSS® Statistics 27 for Windows. Continuous variables are presented as mean $\pm$ standard error of the mean and categorical variables as number and percentage (%). The correlation between variables was estimated using the Rho coefficient of Spearman. Mixed-effects polynomial regression models with restricted maximum likelihood estimation and first-order autoregressive covariance structure were used to examine the differences in CRP levels and WCC between non-infected and infected patient (overall and in sub-groups according to the surgical intervention), and according to the use of CPB or not for CABG patients at 8 time-points, daily from baseline (operation day) to post-operative day 7. Because

the trajectories of CRP level and WCC were unlikely to follow a straight line, we considered up to the third-degree polynomial models of day and their interactions with the group effect were tested. Model checking was performed by inspection of residual and normal plots. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

RESULTS

Among 511 patients screened, 429 patients were included in the study. Reason for the exclusion as indicated in Supplementary material. Clinical data, baseline characteristics and outcomes of the included patients are presented in Table 1. The median EUROSCORE was 1.6 [IQR 3.1]. Overall values and kinetics of CRP and WCC are reported in Table 2. A total of 45 patients (10.5%) developed postoperative infection.

Primary outcomes

The kinetics of CRP and WCC showed significant within-group changes during the first postoperative week,

regardless of the development of postoperative infection. In the overall population, patients developing postoperative infection had higher values of CRP and WCC than those without infection [$P < 0.01$ and $P = 0.02$, respectively; Figures 1 and 2].

As shown in Table 3 (top part), between-groups (infected vs not infected) difference in CRP became significant from postoperative day 2 till day 7. Regarding WCC, significant differences between infected and non-infected patients were visible from postoperative day 3 till day 7 [Table 3, bottom part].

Sub-group analyses

As shown in Table 3, when the analyses of CRP and WCC kinetics were conducted separating the postoperatively infected and non-infected patients in four sub-groups according to the type of surgery, we mostly found non-significant between-group differences in the biomarkers' kinetics. However, this is possibly the result of underpowered analyses as some of them were close the P value cut-off. In particular, CRP analysis

Table 1: Demographics and characteristics of included patients

Baseline patients' characteristics	Count (%)
Sex	
Female	96 (22%)
Male	333 (78%)
Age	
Years (mean±SD)	68±11
Admission type	
Elective	299 (70)
Emergency	130 (30)
Type of surgery	
Isolated CABG on-CPB	169 (39)
Isolated CABG off-CPB	86 (20)
Isolated Valve replacement	90 (21)
Isolated Valve repair	21 (5)
Valve surgery + CABG	63 (15)
Preoperative Left Ventricular function	
Normal	348 (81)
Abnormal	81 (19)
Preoperative Right Ventricular function	
Normal	428 (100)
Abnormal	1 (0,2)
Diabetes	
No	317 (74)
Yes	112 (26)
Smoking History	
No	117 (27)
Yes	97 (23)
Unknown	215 (50)
Hypertension	
No	137 (32)
Yes	251 (58)
Unknown	41 (10)
Hypercholesterolemia	
No	162 (38)
Yes	213 (50)
Unknown	54 (13)

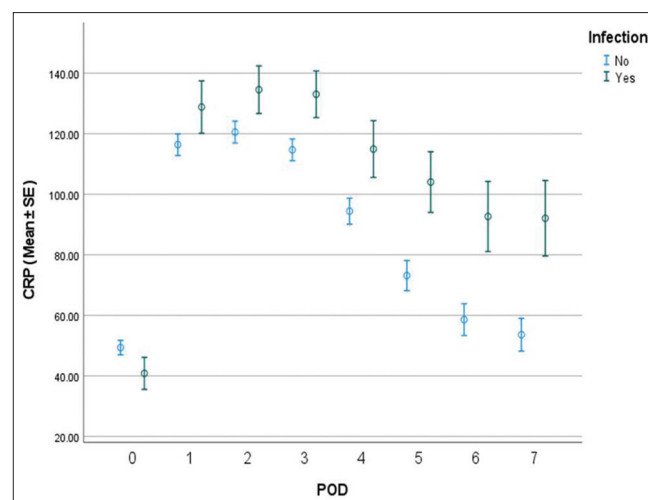


Figure 1: C-Reactive Protein (CRP) kinetics after cardiac surgery comparing patients with or without postoperative infection. POD: Postoperative day. SE: Standard error

Table 2: Overall values and kinetics of C-Reactive Protein (CRP) and White Cell Count (WCC). Results are expressed as mean and standard error (SE)

	POD	CRP			WCC		
		n	Mean	SE of Mean	n	Mean	SE of Mean
	0	346	48.56	2.23	416	11.7	0.2
	1	349	117.72	3.32	421	12.9	0.2
	2	305	122.43	3.33	375	11.4	0.2
	3	295	117.22	3.29	359	9.9	0.2
	4	200	97.85	3.93	235	9.5	0.2
	5	155	79.16	4.55	187	9.8	0.3
	6	132	65.35	4.93	152	10.7	0.3
	7	115	61.00	5.16	132	11.7	0.4

Table 3: C-Reactive Protein (CRP, top half of the table) and White Cell Count (WCC, bottom half of the table) kinetics after cardiac surgery. Groups are analyzed according to presence of infection and type of surgery. Significance is reported as interaction (between groups differences) and as time effect (changes over time within each group). In bold font are indicated the significant difference at 0.05 level. CABG: Coronary bypass artery grafting. CPB: Cardiopulmonary bypass. POD: Postoperative day. N.B. When less than 4 patients were present the value is not reported

CRP Kinetics		POD 0	POD 1	POD 2	POD 3	POD 4	POD 5	POD 6	POD 7	Interaction <i>P</i>
Infection	Surgery	Time Effect <i>P</i>								
NO	All	49.4±2.4	16.4±3.6	120.6±3.6*	114.7±3.6*	94.5±4.3*	73.2±5.0*	58.6±5.3*	53.6±5.4*	<0.01
YES	All	40.9±5.3	128.8±8.7	134.6±7.9	133.1±7.7	115.0±9.4	104.8±10.0	92.7±11.6	92.1±12.5	<0.001
NO	On-CPB CABG	47.9±3.8	108.3±6.0	115.7±6.2	109.1±6.2	90.9±7.1	68.2±8.9	57.2±8.4	47.5±8.4	0.33
YES	On-CPB CABG	34.7±9.6	104.2±19.4	104.3±17.3	107.4±15.7	84.7±18.1	83.2±18.8	63.1±23.4	78.5±21.6	<0.001
NO	Off-CPB CABG	57.9±5	130.3±6.6	131.7±7	134.4±5.5	110.3±9.5	72±11.1	69.3±16.9	51.3±16.4	0.051
YES	Off-CPB CABG	19.3±8.9	130.8±14.6	-	-	136.8±19.3	-	-	-	<0.001
NO	Valve surgery	47.3±4.9	119.8±6.6	121.4±6.6	102.5±7.2	85.9±7.6	69.3±8.7	47.1±7.6	48.8±8.8	0.07
YES	Valve surgery	53.6±8.3	153.4±2.6	155.2±0.8	154.6±1.4	134.8±8	111.9±11.8	86.3±16.5	80.2±27.4	<0.001
NO	CABG + Valve	43.2±6.4	113±10.4	116.8±10.7	124.1±9.2	101.2±12.2	90.5±12.4	79±15.5	78.5±13.7	0.09
YES	CABG + Valve	48.6±8.3	143±9.4	154.1±1.9	148.4±7.6	133.8±13.2	122.4±14.2	128±13.4	115.1±16	<0.001
Secondary Outcome (effects of CPB - not infected pts)										
NO	Off-CPB CABG	57.9±5	130.3±6.6	131.7±7	134.4±5.5	110.3±9.5	72±11.1	69.3±16.9	51.3±16.4	0.55
NO	On-CPB CABG	47.9±3.8	108.3±6	115.7±6.2	109.1±6.2	90.9±7.1	68.2±8.9	57.2±8.4	47.5±8.4	<0.001
WBC count Kinetics		POD 0	POD 1	POD 2	POD 3	POD 4	POD 5	POD 6	POD 7	Interaction <i>P</i>
Infection	Surgery	Time Effect <i>P</i>								
NO	All	11.7±0.2	12.9±0.2	11.3±0.2	9.9±0.2*	9.4±0.2*	9.7±0.3*	10.4±0.4*	11.3±0.4*	0.02
YES	All	12.0±0.7	13.1±0.7	12.2±0.7	10.5±0.5	9.7±0.5	10.5±0.5	12.1±0.7	13.6±1.1	<0.001
NO	On-CPB CABG	11.6±0.3	13.2±0.3	11.6±0.3	10.2±0.3	9.9±0.4	10.3±0.5	10.7±0.5	11.1±0.5	0.53
YES	On-CPB CABG	12.3±1.6	15.4±1.3	14.8±1	12.1±0.8	10.9±0.9	11.3±0.9	12.6±1	13.5±1.4	<0.001
NO	Off-CPB CABG	12±0.5	12.4±0.4	11.2±0.5	9.7±0.4	9.3±0.4	8.9±0.8	10.4±1.6	12.1±1.8	0.64
YES	Off-CPB CABG	13.6±1.8	12.5±0.6	13.1±2.0	10.5±1.9	10.0±1.6	10.5±0.2	12.8±0.1	-	<0.01
NO	Valve surgery	11.4±0.4	12.4±0.4	11±0.4	9.6±0.4	8.7±0.4	9.2±0.5	9.8±0.7	10.7±0.9	0.59
YES	Valve surgery	12±1.1	11.6±0.9	10.4±1.1	10±1.3	8.6±1.1	9.4±1.3	9.4±1.8	11.3±2.9	<0.001
NO	CABG + Valve	12±0.7	13.4±0.7	11.5±0.7	9.7±0.5	10±0.7	10.1±0.8	10.8±0.8	12.1±1.0*	0.04
YES	CABG + Valve	11±0.7	11.4±1.1	9.4±1.2	8.6±0.8	9±0.5	10.5±0.8	13±1.3	14.9±1.8	<0.001
Secondary Outcome										
NO	Off-CPB CABG	12±0.5	12.4±0.4	11.2±0.5	9.7±0.4	9.3±0.4	8.9±0.8	10.4±1.6	12.1±1.8	0.28
NO	On-CPB CABG	11.6±0.3	13.2±0.3	11.6±0.3	10.2±0.3	9.9±0.4	10.3±0.5	10.7±0.5	11.1±0.5	<0.001

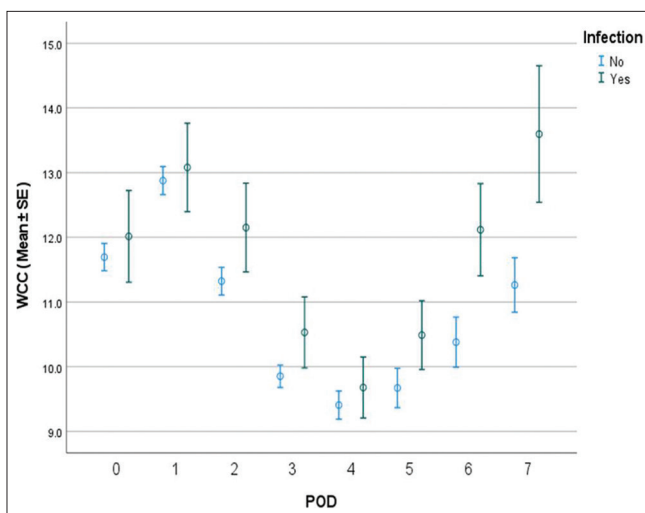


Figure 2: White Cell Count (WCC) kinetics after cardiac surgery comparing patients with or without postoperative infection. POD: Postoperative day. SE: Standard error

according sub-groups showed the following values: On-CPB CABG $P = 0.33$; off-CPB CABG, $P = 0.051$; valvular surgery, $P = 0.07$; on-CABG + valvular surgery,

$P = 0.09$. Regarding WCC analysis according sub-groups we found: On-CPB CABG $P = 0.53$; off-CPB CABG, $P = 0.64$; valvular surgery, $P = 0.59$; on-CABG + valvular surgery, $P = 0.04$. The latter was the only significant result but the difference was significantly different merely at postoperative day 7 (postoperatively non-infected 12.1 ± 1.0 vs infected 14.9 ± 1.8), thus of doubtful clinical value.

Secondary outcome

Regarding the secondary outcome, in the selected population of non-infected patients undergoing CABG, we found no difference in CRP and WCC kinetics between patients undergoing on- vs. off-CPB procedure ($P = 0.55$ and $P = 0.28$, respectively).

Analysis of correlation

For the entire study population, there was a significant correlation of CRP values with SOFA score ($r = -.198$, $P < 0.001$) and with EUROSCORE ($r = -.474$, $P < 0.001$). WCC was not correlated with SOFA score ($r = -.070$, $P = 0.16$) and EUROSCORE ($r = -.096$, $P = 0.051$).

DISCUSSION

We investigated role of commonly used biomarkers in detecting infectious complications in adult patients undergoing cardiac surgery. Kinetics of CRP and WCC were followed during the first postoperative week. We found significant changes in CRP and WCC course during the study period, and patients developing postoperative infection had greater CRP and WCC values than those without infection. In particular, such difference became significant earlier for CRP (from the second postoperative day) as compared to WCC (from the 3rd postoperative day). Therefore, it seems that CRP may provide earlier information in support of decision-making when there is clinical suspect of an ongoing infective process.

In this context, it must be immediately clear that clinical diagnosis of postoperative infection after cardiac surgery represents a significant challenge and biomarkers may be extremely useful. Indeed, fever and other clinical signs and symptoms reflecting an inflammatory response are not specific. For instance, the occurrence of hypotension and/or tachycardia (possibly resembling a condition of septic shock) is common in cardiac surgery patients; indeed, they are often exposed to pharmacological vasoactive drugs not only for the management of their underlying cardiovascular dysfunction, but also in reason of the hemodynamic changes induced by the surgical procedure and by the use of CPB.

As microbiological results (cultures) are not immediately available, biomarkers may be extremely important in supporting the clinical decision to start (or not) an antibiotic therapy and to guide the treatment of a suspected infective process.^[11] Of note, CRP levels increase not only after an infection,^[12] but also after non-infective conditions.^[6] Elevated serum CRP concentrations are correlated with an increased risk of organ failure and death after surgery,^[13] and serial measurements may be useful for identifying the presence of an inflammatory status and for the early detection of infective complications.^[14]

Our study adds knowledge to the body of literature and suggests that CRP may rise earlier than WCC in patients developing postoperative infection. However, the role of CRP in the setting of cardiac surgery is more debated. On one side, it has been suggested that CRP may have a prognostic role being correlated with severity scores (EUROSCORE and SOFA scores);^[15] moreover, several studies have suggested an association between abnormal preoperative CRP values and occurrence of postoperative infections,^[12,16] complications^[17] and/or

mortality.^[16] Conversely, the role of CRP kinetics for the early identification of postoperative infection is more unclear. For instance, Rosmarakis *et al.*^[18] found that an increase of CRP levels can be observed in the first 2-3 postoperative days in patients developing infection after off-CPB CABG. However, other studies demonstrated no predictive value of CRP after on-CPB CABG, with a postoperative increase even in the absence of infection.^[19] These conflicting findings extend also to the setting of pediatric cardiac surgery, where on one side Nahum *et al.*^[20] showed that serial measurements of CRP (and CRP velocity) may assist clinicians in differentiating postoperative fever due to bacterial infection from the noninfectious origin, whilst opposite findings have been found by other studies.^[21,22] To add further complexity, Silveti *et al.*^[23] studied a pediatric population undergoing cardiac surgery with use of CPB and surprisingly found that WCC values at ICU arrival and CRP values at 24 hours were higher in pediatric patients without infections.

A secondary issue investigated by our study (secondary analysis) was the impact of CPB on CRP and WCC kinetics. Indeed, the systemic inflammatory response after cardiac surgery represents an extremely complex process certainly influenced by the use of CPB.^[3,7] Ischemia/reperfusion injury, endotoxemia, contact of the blood components with the artificial surface of the circuit and the surgical trauma *per se* exert synergistic inflammatory effects, making challenging the clinical interpretation of CRP in this specific clinical setting. For this reason, we analyzed the subgroup of non-infected patients comparing those undergoing on-CPB and off-CPB CABG. Our results show no difference in both biomarkers' kinetics according to the use of CPB, results supporting the assumption that CRP is not largely influenced by the institution of CPB; therefore, the decision to monitor postoperatively CRP for early detection of infective complications should be independent from the intraoperative use of CPB or not.

CRP and WCC are routinely measured biomarkers, but PCT is probably superior among the biomarkers for the diagnosis of postoperative infection, not only in terms of predictive value,^[24,25] but also because it peaks earlier (day 1).^[26] Nonetheless, it should be noted that not all studies confirm such early predictive role of PCT for postoperative infection.^[27,28] Moreover, the cost of the immunoassay for PCT is a limit for its widespread routine application.

Other new biomarkers such as endocan^[29] and presepsin^[30] could be useful and deserve to be evaluated in multicenter studies, but their clinical use is still at embryonic level in the field of cardiac surgery.

Limitations

Our study has the strength of collecting data on a relatively large number of patients in two University Hospitals in different countries. However, the study has several limitations. First of all its design is retrospective. Second, in one institution all patients undergoing cardiac surgery with CPB received intravenous steroids. Third, the subgroup analyses according surgery should be interpreted cautiously as the number of samples were limited in most cases and the analyses are consequently underpowered. Indeed, most sub-group analyses did not show differences in the biomarkers' kinetics, though several trends toward significant variations were noted for CRP (with *P* values ranging between 0.05 and 0.09).

CONCLUSION

In the postoperative period after cardiac surgery, CRP and WCC increase more consistently in patients developing postoperative infection. CRP increases one earlier than WCC (day 2 vs day 3, respectively). CRP kinetics does not seem influenced by the institution of CPB in non-infected patients. Prospective research with large multicenter studies is needed to define cut-offs for identification of postoperative infection.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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