

# Reduced complement activation during cardiopulmonary bypass does not affect the postoperative acute phase response

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## Abstract

**Objective:** In the present study the relationship was evaluated between perioperative inflammation and the postoperative acute phase response in patients undergoing elective coronary artery bypass grafting (CABG) assisted by cardiopulmonary bypass (CPB). CPB circuits contained either non-coated- (UMS), Carmeda<sup>®</sup>- (BPS) or Trillium<sup>®</sup>-coated oxygenators (BAS). **Methods:** Prospectively, 71 CABG patients were randomly allocated to one of the oxygenator groups (UMS:  $n=25$ , BPS:  $n=25$  and BAS:  $n=21$ ). Terminal complement complexes (TCC) and elastase were determined in plasma samples collected before, during and after bypass. Secretory phospholipase A<sub>2</sub> (sPLA<sub>2</sub>) and C-reactive protein (CRP) were determined before and after bypass. **Results:** Demographic, CPB and clinical outcome data were similar for the three groups. TCC and elastase increased during CPB, and decreased thereafter. Significant differences between the groups were present in the levels of TCC at the end of CPB ( $P=0.002$ ) and at the first ( $P=0.012$ ) and second ( $P<0.001$ ) postoperative days, the BPS and BAS groups having reduced levels of TCC compared to the UMS group. Also elastase concentrations differed significantly between the groups at the end of CPB ( $P<0.001$ ). The postoperative sPLA<sub>2</sub> and CRP levels increased in all three groups on the first and second postoperative days, but no significant differences were present between the groups. **Conclusions:** Material-induced reduction of the inflammatory response during CPB does not affect the postoperative acute phase response. Thus, in CABG patients this response seems relatively unaffected by the composition and/or biocompatibility of the modern CPB circuit and rather to be evoked by surgical trauma, anesthetics and organ perfusion.

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**Keywords:** Acute phase response; Inflammatory response; Cardiopulmonary bypass; Coronary artery bypass grafting

## 1. Introduction

Patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) develop a systemic inflammatory response leading to an acute phase response with sepsis-like symptoms during the postoperative recovery [1,2]. Factors leading to this systemic inflammatory response are the CPB procedure, the surgical trauma and the necessity for general anesthesia [3].

Cardiac surgery with CPB causes a biphasic complement activation. The first phase occurs during CPB and directly results from the interaction of blood with the extracorporeal circuit. The second phase occurs postoperatively and is characterized by increasing levels of the acute phase proteins secretory phospholipase A<sub>2</sub> (sPLA<sub>2</sub>) and C-reactive protein (CRP) that contribute to complement activation [4,5]. Conversely, the inflammatory reaction during CPB may contribute to the postoperative generation of sPLA<sub>2</sub> and CRP [6]. During surgery and the early postoperative stage, the extent of the inflammatory response is associated with clinical symptoms such as hemodynamic instability, fever, bleeding disorders and organ failure in severe cases [7–9].

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Complement activation, elastase, sPLA<sub>2</sub> and CRP all contribute to the acute phase response [5]. The main function of this response is the reduction of ongoing tissue damage, neutralization of inflammatory agents and the activation of repair processes [10]. Both sPLA<sub>2</sub> and CRP are important acute phase proteins. sPLA<sub>2</sub> levels rise 6–8 h after a challenge such as a surgical procedure, reaching peak values on the first and second postoperative days. CRP levels rise 8–10 h after a challenge, reaching peak values at the second postoperative day. It has been hypothesized that sPLA<sub>2</sub> and CRP, in a combined effort, promote phagocytosis of injured cells and tissue debris [11].

Coatings of the extracorporeal circuits have improved the biocompatibility, resulting in reduced complement activation and activation of white blood cells during and after bypass surgery [12–14]. In the present study, we compared Trillium<sup>®</sup> or Carmeda<sup>®</sup> coated oxygenators with uncoated oxygenators. The Trillium<sup>®</sup> coating is biopassive, developed to act as a non-thrombogenic and biocompatible surface. In contrast, the Carmeda<sup>®</sup> coating is bioactive. This coating exposes functional heparin, that binds to antithrombin and reduces coagulation activation and inflammation. The clinical relevance of coatings, however, on the postoperative performance of patients during the first days after bypass surgery remains subject to debate [12–16]. Therefore, in the present study we analyzed a possible relationship between the perioperative inflammation and the postoperative acute phase response in patients undergoing cardiac surgery.

## 2. Patients, materials and methods

### 2.1. Patients

Prospectively 71 patients who underwent elective coronary artery bypass grafting assisted by CBP were included after signed informed consent had been obtained. Inclusion criteria were age 21–75 years, elective coronary artery bypass surgery, ejection fraction >30%, body surface area >1.66 m<sup>2</sup> and preoperative hemoglobin levels >7.5 mmol/l. Exclusion criteria were combined valve surgery or aneurysmectomy, redo operations, insulin dependent diabetes mellitus, creatinine plasma level >300 µmol/l, preoperative intra-aortic balloon pumping, preoperative use of non-steroid antiinflammatory drugs, preoperative use of warfarin, preoperative immunosuppressive therapy >24 h, allergic reactions and chronic obstructive pulmonary disease. This study was approved by the Medical Ethics Committee of the Academic Medical Center of Amsterdam.

### 2.2. Cardiopulmonary bypass

All extracorporeal bypass circuits contained a hollow fiber oxygenator (Affinity<sup>®</sup>, Medtronic, Minneapolis, MN). The patients were randomly allocated to three groups in

which the oxygenator was either uncoated, i.e. without surface modification (unmodified surface: UMS; *n*=25) or coated with biopassive surface (Trillium<sup>®</sup>; Medtronic: BPS; *n*=25) or bioactive surface (Carmeda<sup>®</sup>; Medtronic: BAS; *n*=21). The additional, non-coated components of the extracorporeal circuit were identical for all patients, and included a soft-shell venous reservoir, two additional reservoirs, an Affinity<sup>®</sup> arterial line filter (38 µm), tubing system (Medtronic) and a roller pump as the arterial blood pump (3M Sarns, Ann Arbor, MI).

The Trillium<sup>®</sup> surface coating has been developed to minimize adsorption of proteins and adherence of cells. This biopassive surface coating consists of a procedure involving two polymers. The first one is a primer and is based upon polyethyleneimine that is modified hydrophobically in order to enhance strong binding to artificial materials. The second polymer is an anionic entity, thus strongly adhering to the cationic primer. It consists of 3 blood compatible functional groups: sulphonate groups, polyethylene oxide (PEO) chains and heparin molecules from a porcine source. Sulphonate groups yield a characteristic anticoagulant effect to polymers by mimicking the functional groups responsible for heparin's anticoagulant action. Moreover, sulphonate groups are negatively charged and they are believed to contribute to thromboresistance. PEO chains are highly hydrophilic and thus minimize the interaction with the aqueous environment. The presence of hydrated PEO chains minimizes protein adsorption. Heparin is modified to copolymerize with sulphonate groups and PEO monomers. Theoretically, the advantage of this coating should not only be related to the presence of heparin, but also caused by endothelium-like properties of the negatively charged surface.

The Carmeda<sup>®</sup> bioactive surface is also based on depositing a polymer coating, polyethyleneimine, onto various types of surfaces. Naturally negatively charged, non-leaching heparin fragments, prepared from the degradation of heparin in nitrous acid, are then endpoint-attached and covalently bound to the polymer. The endpoint attached method assures that the heparin active binding sites are properly oriented to remain free to participate in biological reactions, similar to the orientation of heparan sulfate molecules found on the vascular endothelium. The bioactive coating is developed to provide a thromboresistent blood contact surface to reduce thrombogenesis and activation of the whole body inflammatory response.

Shed blood from the surgical field was collected in one of the additional reservoirs, and processed by a cell saver (HaemoLite 2 plus, Haemonetics Corp., Braintree, MA). Processed blood was returned into the systemic circulation immediately after CPB. Systemic blood from the aortic root cannula was collected in the other reservoir, and returned into the systemic circulation via the soft-shell venous reservoir during the bypass procedure.

The extracorporeal system was primed with 500 ml lactated Ringer's solution, 1 l Haemacell (Behring, Malburg, Germany), 100 ml mannitol 20% (w/v), 50 ml of

sodium bicarbonate 8.4% (w/v) and 200 ml aprotinin ( $2 \times 10^6$  KIU Trasylol; Bayer, Leverkusen, Germany). Magnesium sulphate (4 mmol/10 kg; i.e.  $24 \leq \times \leq 32$  mmol) and 10,000 IU bovine heparin (Leo Pharmaceutical Products, Weesp, The Netherlands) were added to the priming solution.

All patients received 300 IU/kg heparin (Leo Pharmaceutical Products, Weesp, The Netherlands) before cannulation of the aorta. Systemic heparinization was monitored at fixed time intervals before onset and during CPB, additional heparin was administered when required. Moderate hypothermia (30–34 °C) was applied to all patients. Myocardial protection was achieved using cold (4–8 °C) crystalloid cardioplegia solution (St Thomas). After weaning from CPB and decannulation, heparin was neutralized with protamine sulphate at a 1:1 ratio.

### 2.3. Blood sampling and processing

Blood samples were collected before bypass after induction of anesthesia, 15 min after start CPB, at the end of CPB, 30 min after administration of protamine sulphate and on the first and second postoperative day. All blood samples were drawn from the arterial line. For comparison between plasma samples, terminal complement complexes (TCC), elastase and white blood cell counts were all corrected for hemodilution by hemoglobin concentration. Blood was collected at the indicated sample times and cell-free plasma was prepared by centrifugation for 20 min at  $1550 \times g$  and 20 °C and stored at –80 °C until analysis. TCC (Quidel, San Diego, CA), elastase (Diagnostics Products Corporation, DPC Biermann GmbH, Bad Nauheim, Germany), sPLA<sub>2</sub> (Roche Diagnostics, Mannheim, Germany) and CRP (DAKO, Glostrup, Denmark) were all determined by ELISA according to the manufacturer's instructions. Preliminary observations showed no or limited increase of sPLA<sub>2</sub> and CRP levels during the operation [4,6, 11,17], and because peak values of sPLA<sub>2</sub> and CRP are known to occur at the first and second postoperative days, perioperative samples were not analyzed for these markers. Blood samples for white blood cell counts and hemoglobin were collected in 5 ml glass vacutainer tubes containing EDTA (Becton Dickinson (BD), San Jose, CA), and analyzed on a CellDyn 4000 (Abbot, Mijdrecht, The Netherlands).

### 2.4. Statistics

Data were analyzed using SPSS, release 11.0 (SPSS Inc., Chicago, IL). Demographic, CPB and clinical data are reported as means with standard deviations or medians with interquartile ranges. Biochemical data, corrected for hemodilution, are presented as median values with interquartile ranges. Comparisons between groups were made by the Kruskal–Wallis Test. Conditional on statistical significance of the Kruskal–Wallis test, we performed Mann–Whitney *U*-tests for pair wise comparison of

treatment groups. For all biochemical data, statistical analyses were performed on the change ( $\Delta$ ) of that variable relative to the baseline value ( $t=0$ ) per patient. Statistical significance ( $P < 0.05$ , 2-sided) is indicated.

## 3. Results

### 3.1. Clinical results

No differences were present between the patient groups for any of the preoperative parameters investigated (Table 1). The clinical outcome data are summarized in Table 2. No significant differences were established between the three groups concerning the clinical outcome. Similarly, we found no differences in white blood cell counts and hemoglobin concentrations between the groups at any sampling time (data not shown).

### 3.2. Complement activation and elastase

Before CPB, complement activation by release of TCC was not detectable in any of the three groups. Plasma concentrations of TCC increased in all three groups of patients 15 min after the onset of CPB. Concentrations of TCC further increased in all three groups during CPB, and remained elevated after protamine sulphate administration. On the first and second postoperative day, the TCC concentrations decreased markedly although preoperative baseline values were (still) not reached. Significant differences between the groups were observed at the end of CPB ( $P=0.002$ ), and at the first ( $P=0.012$ ) and second ( $P < 0.001$ ) postoperative day. The BPS and BAS groups showed reduced levels of TCC compared to the UMS group

Table 1  
Demographic and CPB data

	Surface modification of the oxygenator		
	Uncoated (UMS)	Biopassive surface (BPS)	Bioactive surface (BAS)
Patient number	25	25	21
Male/female	25/0	23/2	20/1
Age (years)	62.0 ± 7.1 <sup>a</sup>	59.9 ± 9.7	61.4 ± 9.9
Body weight (kg)	87.5 ± 12.1	87.1 ± 14.8	83.1 ± 9.8
Body surface area (m <sup>2</sup> )	2.04 ± 0.17	2.06 ± 0.18	1.99 ± 0.12
White blood cell count (10 <sup>9</sup> /l)	6.9 ± 2.0	6.3 ± 1.7	6.3 ± 2.0
Hemoglobin (mmol/l)	8.5 ± 0.6	8.4 ± 0.7	8.3 ± 0.5
Cardiopulmonary bypass (min)	93.5 ± 21.8	85.1 ± 21.4	95.4 ± 24.2
Aortic cross-clamping (min)	58.5 ± 15.9	55.1 ± 17.2	58.6 ± 19.7
Distal anastomoses	4.4 ± 1.2	4.0 ± 1.2	4.1 ± 1.2

<sup>a</sup> All data are presented as mean ± SD. No significant differences were found between the groups for any of the parameters. The internal mammary artery was used in all patients.

Table 2  
Clinical outcome data

	Surface modification of the oxygenator		
	Uncoated surface (UMS; n = 25)	Biopassive surface (BPS; n = 25)	Bioactive surface (BAS; n = 21)
Blood loss 18 hrs ICU (ml) <sup>a</sup>	665 (507–992)	700 (552–1105)	870 (735–1415)
Number of patients reexplored for bleeding	0/25	0/25	0/21
Required blood products in the ICU			
Red blood cells (units)	20	20	23
Number of patients receiving red blood cells	9/25	12/25	12/21
Fresh frozen plasma (units)	19	17	35
Number of patients receiving fresh frozen plasma	8/25	5/25	11/21
Platelets (units)	1	3	3
Number of patients receiving platelets	1/25	3/25	3/21
Highest CK-MB massa (µg/ml) <sup>a</sup>	13 (11.8–19.8)	18.3 (11.6–35.8)	14.4 (9.1–21)
Intubation time > 48 h (number of patients)	5/25	5/25	2/21
Renal dialysis (number of patients)	0/25	1/25	0/21
ICU stay > 10 days (number of patients)	1/25	2/25	0/21
ICU stay (h) <sup>a</sup>	22 (21–78)	24 (19–67)	27 (21–75)
Mortality (number of patients)	0/25	0/25	0/21
Hospital stay (days) <sup>a,b</sup>	5 (5–7)	6 (5–7)	6 (5–8)

<sup>a</sup> Data are presented as median (interquartile ranges). No significant differences were found between the groups.

<sup>b</sup> Number of days from the operation until discharge back to the referring hospital. None of the 71 patients included in the present study required either an intra-aortic balloonpump or a left ventricle assist device.

(end CPB: BPS  $P=0.001$ , BAS  $P=0.024$ ; at the first day ICU: BAS  $P=0.007$ ; at the second day ICU: BPS  $P=0.001$ , BAS  $P<0.001$ ; Fig. 1).

The elastase levels also increased in all three treatment groups during bypass. The postoperative elastase levels decreased, but still remained higher than the baseline values. Significant differences between the groups were found at the end of CPB ( $P<0.001$ ). The levels of elastase were reduced in the BPS and BAS groups compared to the UMS group (BPS  $P=0.046$  and BAS  $P<0.001$ ; Fig. 2). The reduced elastase levels in the BPS and BAS groups were not due to decreased numbers of circulating white blood cells, since the overall white blood cell counts were similar in the three patient groups and remained constant at any sample time (data not shown).

### 3.3. Secretory phospholipase A<sub>2</sub> (sPLA<sub>2</sub>) and C-reactive protein (CRP)

sPLA<sub>2</sub> and CRP levels increased in all three groups on the first day ICU when compared to preoperative baseline values. On the second postoperative day both values further increased. No significant differences were present between the groups (Figs. 3 and 4). sPLA<sub>2</sub> levels on the first day in the ICU in the BAS group tended to be reduced compared to the UMS group, but on the second day in the ICU this tendency disappeared almost completely.

## 4. Discussion

The present study shows that although the use of coated oxygenators reduces the intra-operative inflammatory

response when compared to the uncoated oxygenators, the postoperative acute phase response is comparable in these groups. Coatings have improved the overall biocompatibility of extracorporeal circuits, as for instance reflected by reduced (intra-operative) complement activation. Whether or not these improvements have significantly

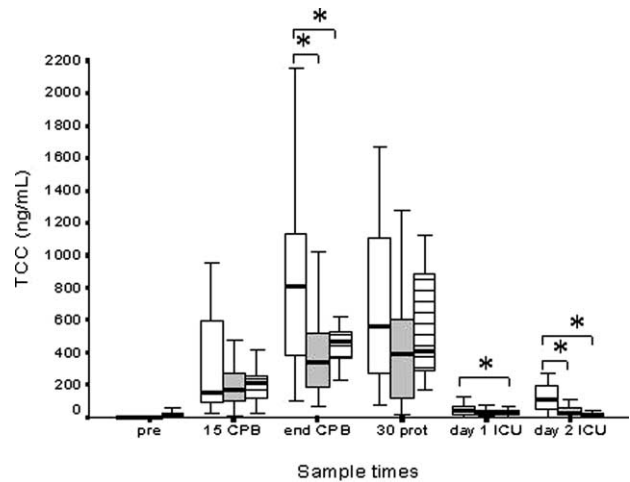


Fig. 1. Concentrations of terminal complement complexes (TCC) in patients undergoing elective CABG. TCC concentrations before bypass after induction of anesthesia (baseline value; pre), 15 min after start bypass (15 CPB), at the end of bypass after release of the aortic cross-clamp (end CPB), 30 min after administration of protamine sulphate (30 prot), day 1 and day 2 ICU. Shown are TCC concentrations in patients treated with either an uncoated oxygenator (unmodified surface [UMS; n = 25, white bars]), an oxygenator coated with a biopassive surface [BPS; n = 25, grey bars] or an oxygenator coated with a bioactive surface [BAS; n = 21, striped bars]. Medians and interquartile ranges are presented. Asterisks indicate significant differences between the treatment groups ( $P<0.05$ ).

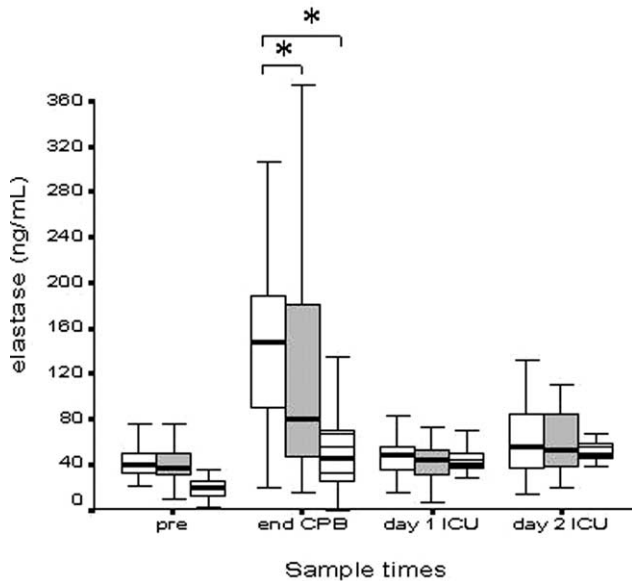


Fig. 2. Concentrations elastase in patients undergoing elective CABG. Elastase concentrations before bypass after induction of anesthesia (baseline value; pre), at the end of bypass after release of the aortic cross-clamp (end CPB), day 1 and day 2 ICU. The measurements were made in patients treated with either an uncoated oxygenator (unmodified surface [UMS;  $n=25$ , white bars]), an oxygenator coated with a biopassive surface [BPS;  $n=25$ , grey bars] or an oxygenator coated with a bioactive surface [BAS;  $n=21$ , striped bars]. Medians and interquartile ranges are presented. Asterisks indicate significant differences between the treatment groups ( $P < 0.05$ ).

contributed to relevant postoperative clinical benefits, is unclear [4,12–14,18].

Although previous investigations showed that the contact between blood and the artificial surfaces of the extracorporeal circuit triggers inflammation [2,7,8,12,

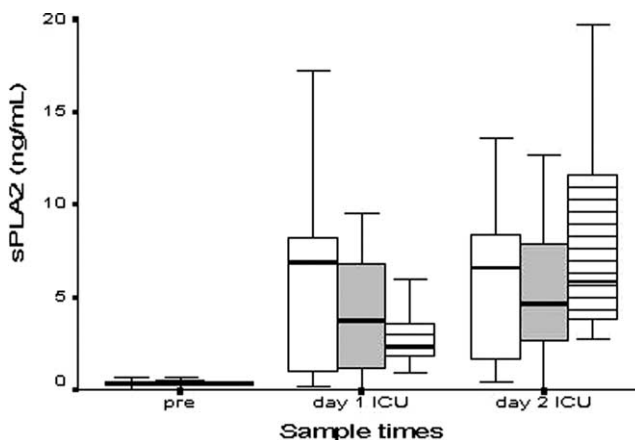


Fig. 3. Secretory phospholipase A<sub>2</sub> (sPLA<sub>2</sub>) in patients undergoing elective CABG. Concentrations of sPLA<sub>2</sub> before bypass after induction of anesthesia (baseline value; pre) and day 1 and day 2 ICU. The measurements were made in patients treated with either an uncoated oxygenator (unmodified surface [UMS;  $n=25$ , white bars]), an oxygenator coated with a biopassive surface [BPS;  $n=25$ , grey bars] or an oxygenator coated with a bioactive surface [BAS;  $n=21$ , striped bars]. Medians and interquartile ranges are presented. No significant differences were present between the three oxygenator groups.

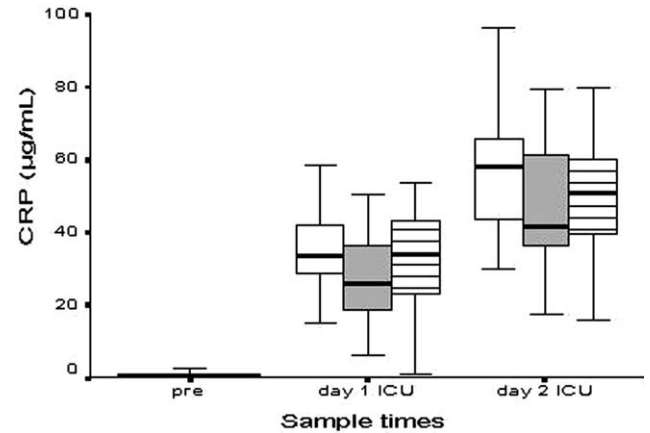


Fig. 4. Concentrations of C-reactive protein (CRP) in patients undergoing elective CABG. Concentrations of CRP before bypass after induction of anesthesia (baseline value; pre) and day 1 and day 2 ICU. The measurements were made in patients treated with either an uncoated oxygenator (unmodified surface [UMS;  $n=25$ , white bars]), an oxygenator coated with a biopassive surface [BPS;  $n=25$ , grey bars] or an oxygenator coated with a bioactive surface [BAS;  $n=21$ , striped bars]. Medians and interquartile ranges are presented. No significant differences were present between the three oxygenator groups at any sample time.

13,19,20], more recent studies also focussed on the role of tissue injury, aortic cross-clamping, hypoperfusion, ischemia and the heparin–protamine sulphate complex in intra-operative complement activation during major surgery [1–3,16]. Fransen et al. [3] demonstrated that postoperative concentrations of CRP were similar in patients undergoing CABG either with or without the assistance of CPB. This strongly suggests that not the CPB circuit itself but the surgical procedure may be the major initiator of the postoperative acute phase response. Accordingly, it so far remains unclear to which extent the direct contact between blood and the surface of the modern extracorporeal circuit may have contributed to the overall postoperative acute phase response. In this study, only the oxygenator was coated. Coating of the entire CPB circuit instead of just the oxygenator may result in greater beneficial effects. However, the oxygenator comprised about 78% of the total surface area of the extracorporeal circuit. Moreover, the non-oxygenator part of this circuit was identical for all patients studied. Therefore the contribution of this non-coated part of the extracorporeal circuit to blood activation was not taken into consideration.

It is well known, that the complement system is highly activated in wound blood [21]. Therefore, in the present study the wound blood was collected separately from the systemic blood and processed by a cell saver before being returned into the systemic circulation (immediately after CPB). Consequently, the intra-operative levels of complement activation and elastase release in our study were not affected by retransfusion of wound blood during the surgical procedure. To which extent the oxygenator coating and the retransfusion of processed cell saver blood contribute to the postoperative levels of complement

activation, elastase and acute phase proteins, remains to be determined. Nevertheless, the material-induced reduction of complement activation during bypass is still observed on the ICU. Thus, the positive effects of coatings that occur during bypass are still observed after bypass despite retransfusion, suggesting that the (possible) contribution of retransfused blood to, e.g. complement activation does not entirely overrule the positive effect of the coating.

In the present study, only elective CABG patients were included. It remains unclear, however, to which degree the improved biocompatibility of the extracorporeal systems reduces the postoperative acute phase response in patients needing complicated and extended cardiac surgery. Because these patients suffer from increased tissue injury, are subjected to extended aortic cross-clamping and perfusion times, and to prolonged general anesthesia and ischemia, the benefits of coatings of modern extracorporeal circuits may be limited.

In conclusion, the postoperative acute phase response appears not to be reduced despite improved biocompatibility of the CPB system in elective CABG patients.

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