

## Original Articles

# Impact of a Phosphorylcholine-Coated Cardiac Bypass Circuit on Blood Loss and Platelet Function: A Prospective, Randomized Study

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**Abstract:** Platelet dysfunction due to cardiopulmonary bypass (CPB) surgery increases the risk of bleeding. This study analyzed the effect of a phosphorylcholine (PC)-coated CPB circuit on blood loss, transfusion needs, and platelet function. We performed a prospective, randomized study at Strasbourg University Hospital, which included 40 adults undergoing coronary artery bypass graft surgery (CABG) ( $n = 20$ ) or mitral valve repair ( $n = 20$ ) using CPB. Patients were randomized either to PC-coated CPB or uncoated CPB (10 CABG patients and 10 mitral valve repair patients in each group). Blood loss and transfusion needs were evaluated intra- and postoperatively. Markers of platelet activation and thrombin generation were measured at anesthesia induction, at the beginning and end of CPB, on skin closure, and on days 0, 1, and 5. Comparisons were made by Student's  $t$  test or covariance analysis (significance

threshold  $p \leq .05$ ). Blood loss was significantly lower in the PC group during the first 6 postoperative hours ( $171 \pm 102$  vs.  $285 \pm 193$  mL,  $p = .024$ ), at the threshold of significance from 6–24 hours ( $p = .052$ ), and similar in both groups after 24 hours. During CPB, platelet count decreased by 48% in both groups. There was no difference in markers of platelet activation, thrombin generation, or transfusion needs between the two groups. Norepinephrine use was more frequent in the control group (63% vs. 33%) but not significantly. PC-coating of the CPB surface reduced early postoperative bleeding, especially in CABG patients, but had no significant effect on platelet function because of large interindividual variations that prevented the establishment of a causal relationship. **Keywords:** platelet dysfunctions, blood loss, cardiac surgery, cardiopulmonary bypass. JECT. 2012;44:5–9

Cardiopulmonary bypass (CPB) surgery carries a risk of excessive bleeding of 5–20% (1). About 30–50% of patients receive labile blood products despite appropriate perioperative anticoagulant and antiplatelet treatment, intraoperative administration of antifibrinolytic drugs, and use of a cell-saving device to treat pericardial suction blood (2,3). In over 50% of cases, the cause of bleeding is not found on revision surgery (1). The major cause seems to be CBP-related quantitative and/or qualitative platelet defects (1,4–13).

Surface coating of extracorporeal circuits in cardiac surgery may help spare platelets, diminish clotting factor activation, and reduce inflammatory response and hemolysis. Phosphorylcholine (PC) polymers reduce protein adsorption and cell attachment (platelets and polynuclear neutrophils) by mimicking the biologically inert surface of blood cells. The first results were published in dogs in 1999 and showed a decrease in platelet and complement activation (13). However, only five studies have been performed in humans since 2000 (14–18). Their results are conflicting.

The aim of this prospective, randomized study was to compare the impact of a PC-coated CBP circuit versus a conventional circuit on perioperative blood loss and transfusion requirements in patients undergoing a coronary artery bypass graft (CABG) or mitral valve repair (MVR).

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Sorin Group provided material (phosphorylcholine-coated circuits) and financial support (biological dosages) for this study.

## PATIENTS AND METHODS

### Study Design and Setting

This prospective, randomized, single-blind, controlled study was performed in the cardiac surgery department between June 2006 and February 2008. The study was approved by the institution's Ethics Committee. All patients gave their written informed consent.

### Patients

Patients aged between 18 and 80 years and scheduled for CABG or MVR were included in the study. Exclusion criteria were pregnancy, ejection fraction <40%, preoperative hemoglobin <11 g/dL, abnormal preoperative blood clotting test results, interruption of antiplatelet drug treatment for <4 days, ongoing anticoagulant treatment, type I or II diabetes, creatinine >200  $\mu\text{mol/l}$ , unstable angina or acute mitral regurgitation, preoperative circulatory support, combined valve and coronary surgery, re-dox surgery, and MVR failure followed by replacement with a biological or mechanical valve.

### Interventions

Patients were randomized into two groups, each made up of 10 patients undergoing MVR and 10 patients undergoing CABG: 1) A control group in which a conventional type D 903 Avant Standard circuit (Sorin, Italy) was used and 2) a PC group for which the circuit had been coated with PC. Intravenous anesthesia induction was with sufentanil, etomidate, and pancuronium bromide. Anesthesia maintenance was with sufentanil and sevoflurane, and with propofol during CPB.

The following were monitored intraoperatively: electrocardiographic pattern (at least two leads), heart rate, ST-segment (automatic monitoring), systemic blood pressure, oxygen saturation (pulse oximetry), central venous pressure, left-atrial pressure, carbon dioxide (capnography), inspiratory and expiratory fraction of the fresh gas delivered by the respirator, oxygen inspiratory fraction of the fresh gas, hourly diuresis, bladder and esophageal temperatures, bispectral index, Activated Clotting Time (ACT) (Hemochron Jr<sup>®</sup>, ITC, Edison, NJ), arterial blood gases, hemoglobin, hematocrit, potassium, and blood sugar every 45 minutes.

Aprotinin was used as an antifibrinolytic agent (initial bolus of 200,000 units followed by a continuous infusion of 50,000 units/h until skin closure). The CBP circuit was primed with 1500 mL of a mixture of Ringer lactate and hydroxyethylstarch (Voluven<sup>®</sup> Fresenius, Germany) to which 200 mL aprotinin and 5000 units of unfractionated heparin were added. A 3 mg/kg heparin bolus was administered before aortic cannulation and supplemented as needed by additional heparin doses during CPB to achieve an ACT >400 seconds. After decannulation, protamine was infused (dose for dose) to antagonize the anticoagulant

effect of the heparin. If the ACT value was 10% above the preheparin value, the patient received a protamine bolus.

The activated blood in contact with the air during CPB and the blood purged from the CPB circuit after decannulation was treated with a cell saver (Electa<sup>®</sup>, Sorin, Italy) and reinfused, thus limiting inflammatory response and hemostatic disorders and enabling better evaluation of the impact of PC-coating on coagulation activation. Body temperature was maintained between 28°C and 34°C throughout CPB. Homologous and/or autologous packed red blood cells were transfused if hematocrit fell below 25% during CBP and below 28% post-CBP, and if postoperative hemoglobin was <10 g/dL.

MVR patients received antiplatelet agents 6 hours after surgery and CABG patients received a low-molecular weight heparin between 12 and 24 hours after surgery.

### Outcome Measures

The following data were recorded perioperatively: CPB circuit priming volume and solute used (Ringer<sup>®</sup> Fresenius, Kabi, France, colloids), total volume of cardioplegic solution, lowest temperature, intraoperative blood loss (compress weighing and surgical suction), consumption of blood products, blood volume treated and returned by the cell saver, hematocrit, and type and dosage of any inotropes used. The duration of anesthesia, CBP, aortic clamping, and surgery were recorded. Postoperatively, blood loss (chest drainage) and number of units of blood products administered were recorded every 6 hours over the first 48 postoperative hours.

The following standard blood parameters were measured at anesthesia induction and on days 0, 1, and 5 during recovery in the intensive care unit: occlusion time, activated partial thromboplastin time, thrombin time, prothrombin time, fibrinogen, platelet count, euglobulin lysis time, and haptoglobin.

Markers of platelet activation [soluble glycoprotein V (GPV) and platelet factor 4 (PF4)], as well as thrombin generation [prothrombin 1 + 2, thrombin-antithrombin complexes (TAT)] were also measured. These measurements were made at anesthesia induction, 30 minutes after the beginning of CBP, at the end of CPB, and on skin closure. GPV was measured by enzyme-linked immunosorbent assay (ELISA) immunoassay (Asserachrom<sup>®</sup> sGPV; Diagnostica Stago, Asnières-sur-Seine, France). The normal range in adults is 10–60 ng/mL (19). PF4 was measured by ELISA immunoassay (Asserachrom<sup>®</sup> PF4, Diagnostica Stago). Normal plasma PF4 values range from 3–8 ng/mL (20). F1 + 2 and TAT were measured on citrated blood in microtitration immuno-enzymatic tests [Enzygnost<sup>®</sup> F1 + 2 (monoclonal) and TAT micro; Dade Behring Marburg GmbH, Germany], based on the sandwich principle (21,22). The reference field

was 69–229 pmol/L for F1 + 2 and 1.0–4.1 µg/L for TAT. The measurement fields were 20–1200 pmol/L and 2–60 µg/L, respectively.

**Statistical Analysis**

Continuous variables were compared by Student’s *t* test and repeat measures by covariance analysis. Ninety-five percent confidence intervals were calculated. The significance threshold was <.05. SPSS software, version 11 (SPSS, Inc., Chicago, IL) was used.

**RESULTS**

**Patient Characteristics**

Forty patients (mean age: 59 years; range: 43–78) were included in the study. Patient demographics and surgical data were similar in the PC and control groups (Table 1).

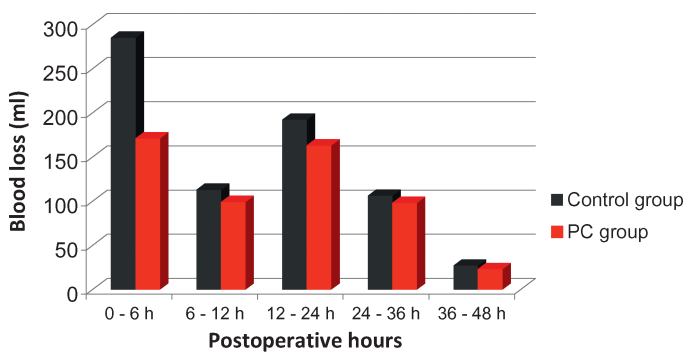
**Blood Loss and Transfusion Requirements**

Blood loss was significantly lower in the PC group than in the control group during the first 6 postoperative hours [171 ± 102 mL (95% confidence interval 124–217) vs. 285 ± 194 mL (95% confidence interval 191–378), *p* = .024]. Blood loss remained lower in the PC group from 6–24 hours postoperatively but the difference had only borderline significance (*p* = .052). After 24 hours, blood loss was similar in both groups (Figure 1). There was no

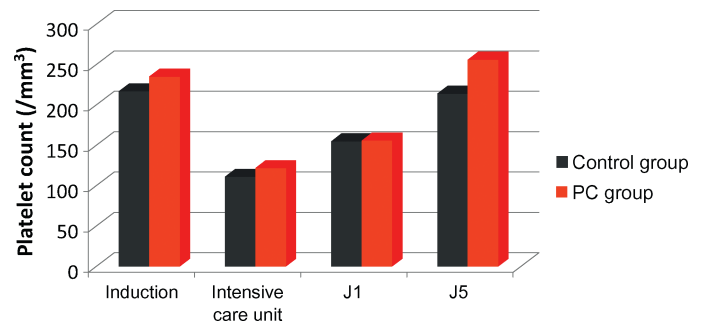
**Table 1.** Demographic and perioperative data.

	Controls ( <i>n</i> = 20)	PC-Coating ( <i>n</i> = 20)	<i>p</i> Value
Age (years)	57 ± 8	60 ± 10	.191
Body mass index (kg/m <sup>2</sup> )	26 ± 3	27 ± 4	.144
Duration of CPB (min)	100 ± 25	91 ± 25	.263
Duration of aortic clamping (min)	67 ± 21	56 ± 17	.106
Lowest temperature (°C)	32.9 ± 1.5	33.0 ± 1.0	.807
Cardioplegia volume (mL)	1652 ± 540	1555 ± 719	.634
Treated blood volume (mL)	4475 ± 2233	3966 ± 1926	.444
Reused blood volume (mL)	1598 ± 1106	1445 ± 876	.627

Values are means ± SD.



**Figure 1.** Postoperative blood loss.



**Figure 2.** Platelet count.

difference in the number of units of blood products transfused either intra- or postoperatively.

Blood loss during the first 12 postoperative hours depended significantly on the type of surgery (MVR or CABG): it was more pronounced in CABG patients (*p* = .025). Blood loss was 36% higher in patients who underwent CABG than MVR when the CBP circuit was uncoated, and 26% higher when it was PC-coated.

**Platelet Function**

Platelet count fell by 48% in both groups during CPB but rapidly returned to normal 24 hours after surgery (Figure 2). The type of surgery (CABG or MVR) had no impact on thrombocytopenia. No significant difference between groups was observed in the markers of platelet activation or thrombin generation (Tables 2–5).

**Other Variables**

Results for the other biological variables (hemoglobin, hematocrit, ACT, prothrombin time, activated partial thromboplastin time, fibrinogen, euglobulin lysis time, and D-dimer) were similar in both groups. The difference

**Table 2.** PF4 kinetic.

	Control Group: Mean Value (SE) ng/mL	PC Group: Mean Value (SE) ng/mL
Induction	6 (6.4)	9.9 (17.6)
CPB 30 minutes	114.8 (166.3)	59.2 (58.6)
End of CPB	144.7 (274.5)	67.2 (106.9)
Skin closure	17.1 (18.8)	17.6 (23.7)

*p* value is not significant.

**Table 3.** GPVs kinetic.

	Control Group: Mean Value (SE) ng/mL	PC Group: Mean Value (SE) ng/mL
Induction	23.8 (6.9)	22.4 (8.3)
CPB 30 minutes	25.7 (13.6)	18.8 (7.0)
End of CPB	46.9 (31.8)	26.0 (11.5)
Skin closure	46.6 (27.7)	38.8 (39.0)

*p* value is not significant.

**Table 4.** F1 + 2 kinetic.

	Control Group: Mean Value (SE) µg/L	PC Group: Mean Value (SE) µg/L
Induction	1.2 (.57)	1.3 (1.2)
CPB 30 minutes	1.5 (.6)	1.7 (1.0)
End of CPB	2.4 (1.4)	2.2 (1.7)
Skin closure	2.6 (1.0)	2.4 (1.3)

*p* value is not significant.

**Table 5.** TAT kinetic.

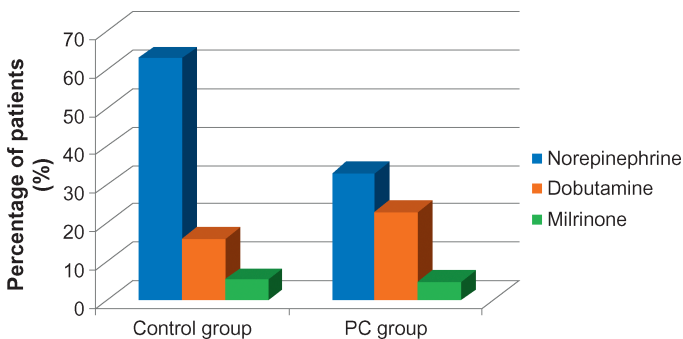
	Control Group: Mean Value (SE) µg/L	PC Group: Mean Value (SE) µg/L
Induction	4.2 (3.4)	7.3 (8.7)
CPB 30 minutes	4.6 (2.0)	7.3 (6.5)
End of CPB	10.9 (8.2)	13.4 (15.3)
Skin closure	12.4 (6.7)	17.4 (17.2)

*p* value is not significant.

in post-CBP catecholamine support was not significantly different between the two groups although norepinephrine use was more frequent in the control than PC group (63% vs. 33% of patients;  $p = .058$ ) (Figure 3). The duration of mechanical ventilation was similar in the control and PC group ( $13.6 \pm 6$  vs.  $11 \pm 47$  hours,  $p = .154$ ), as was the length of stay in the intensive care unit ( $44.6 \pm 7$  vs.  $42 \pm 15.5$  hours,  $p = .525$ ).

## DISCUSSION

Our study has shown that the use of a PC-coating of the CPB circuit resulted in a significant beneficial impact on blood loss during the first 6 hours after CPB surgery. Blood loss remained lower during the first 24 postoperative hours. The benefit was more pronounced during CABG surgery compared with mitral valve repair. These findings support those of De Somer et al. (14) who found a significant decrease in bleeding in the PC group during the first 4 postoperative hours.

**Figure 3.** Perioperative amines support.

Despite the decrease in early postoperative blood loss with the PC-coated CPB circuit, transfusion requirements did not differ in the PC and control groups, possibly because of a bias in patient selection. Our study exclusion criteria meant that our included patients had a low perioperative bleeding risk. A clinical benefit in terms of transfusion requirements and postoperative morbidity may only be found in patients at high risk of bleeding.

Excessive postoperative bleeding may be due either to imperfect surgical hemostasis or to a persistent well-known CPB-related biological disorder. PC-coating may have had a significant beneficial effect on platelet function before spontaneous correction of hemostasis occurred. Platelet alpha-granule contents are normally renewed within 4 hours of CPB, and GpIIb/IIIa and GPIb receptor expression on the platelet surface returns to baseline within 6 hours of decannulation (1). Most revision surgery for early postoperative bleeding takes place during this period when platelet function returns to normal.

A similar drop in platelet count from the first minutes of starting CPB in both groups was observed, as described in other works (1,5,6). Contact between blood cells and the CPB circuit surface has an adverse effect on coagulation. Thrombin increases 20-fold during the first 5 minutes of CPB. It also peaks at decannulation, on reperfusion of the ischemic myocardium, and on protamine administration, but returns to its initial level within 2 hours of CPB (23,24). High thrombin generation leads to platelet, fibrinogen, and clotting factor consumption, which increases the risk of bleeding (25). Many factors can increase thrombin generation, such as blood contamination by lipid and cell debris, air-blood contact, and no treatment of blood harvested from the surgical field, which is a major cause of coagulation activation during CPB (26).

Whether the circuit was PC-coated or not did not significantly influence the kinetics of the two markers of thrombin generation (F1 + 2 and TAT) when activated blood was treated with the cell saver, confirming published observations (26,27). The increase in TAT and F1 + 2 during CPB was moderate in both groups.

The increases observed in our study in PF4 and soluble GPV reflect different stages of platelet activation by thrombin, which occurs within minutes of starting CPB. PF4 is released from alpha-granules of activated platelets. It has a very short half-life (<5 minutes) and strong antiheparin activity. De Somer et al. showed that the plasma PF4 level did not change in the PC group during CPB whereas it doubled in the control group (19). In contrast, no significant difference was observed in the present study, however. In neither De Somer et al.'s study nor ours was the difference significant, probably because of the wide scatter in PF4 values and small patient numbers. GPV is cleaved from the GPIb-V-IX receptor by thrombin during platelet activation. A soluble fragment



is released into the plasma, which reflects changes in the platelet membrane before platelet adhesion to the subendothelium (20,28). In our study, soluble GPV increased between 30 minutes of starting CBP and stopping the pump. There was no significant difference between the two groups.

Finally, extracorporeal perfusion has an inflammatory impact, which can induce a more or less severe vasoplegia syndrome. The PC-coating may reduce this inflammatory reaction as shown by the fact that the need for post-CBP norepinephrine was less frequent in the PC group.

In conclusion, our study has provided evidence for a significant impact of PC-coating of the CBP circuit on blood loss during the first 6 postoperative hours that may be prolonged to 24 hours. However, the small sample size did not enable us to relate this decrease in bleeding to platelet activity. A study on a larger population is required. Moreover, it would be interesting in the future to include patients at high risk of bleeding to establish whether the decreased blood loss in the PC group has a clinical impact on transfusion requirements.

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