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Original Article / Özgün Makale

Phosphorylcholine-coated extracoporeal circulation systems affect coagulation factors during cardiopulmonary bypass insufficiently: a preliminary report

Fosforilkolin kaplı ekstrakorporeal dolaşım sistemleri koagülasyon faktörlerini yetersiz düzeyde etkiler: Ön rapor

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Background: This study aims to investigate the efficacy of the phosphorylcholine (PC)-coated extracorporeal circulation (ECC) circuits compared to the non-coated ECC circuits in patients undergoing isolated coronary artery bypass grafting (CABG).

Methods: Twenty-eight patients (24 males, 4 females; mean age 62±12 years; range 41 to 84 years) who underwent elective CABG due to ischemic heart disease were enrolled in this single-blind prospective study with the odd-even number of randomization method. Phosphorylcholine-coated ECC systems were used in group 1 and non-coated ECC systems were used in group 2. The percentage of the coagulation factor activations [factor (F)-II, F-V, F-VII, F-VIII, F-X, F-XII, and von Willebrand factor], D-dimmer, and anti-thrombin III levels were measured preoperatively, intraoperatively and postoperatively.

Results: The percentage of activation of F-II and F-X in group 1 were significantly higher than group 2 before the cross-clamp removal (T_1) ($p<0.05$). The percentage of activation of factor XII after surgery (six hours later-T_3, postoperative first week-T_4) increased in both groups, however, this increase was significantly higher in group 2 than group 1 ($p<0.01$). D-Dimer levels gradually increased in both groups and remained significantly higher ($p<0.001$), however, no difference was observed between the groups. The antithrombin III activity significantly reduced in both groups at T_1 compared to the baseline values (T_0) ($p<0.01$). The von Willebrand factor activity increased significantly in both groups at T_1 and after termination of cardiopulmonary bypass (T_2) ($p<0.01$), indicating no significant difference between the two groups ($p>0.05$).

Conclusion: Although the percentage of activation of the factors is higher in non-coated ECC systems compared to PC-coated ECC systems, it does not indicate significant clinical differences. In addition, both PC-coated or non-coated ECC systems exert similar biological effects during cardiopulmonary bypass.

Keywords: Blood coagulation factor; extracorporeal circulation; hemocompatibility; phosphorylcholine.

Amaç: Bu çalışmada izole koroner arter baypas greftleme (KABG) yapılan hastalarda fosforilkolin (FK) kaplamalı ekstrakorporeal dolaşım (EKD) devrelerinin, kaplamasız EKD devrelerine kıyasla, etkinliği araştırıldı.

Çalışma planı: Elektif KABG'ye alınan 28 hasta (24 erkek, 4 kadın; ort. yaş 62±12 yıl; dağılım 41-84 yıl) bu tek-kör prospektif çalışma planında ve tek-çift sayı randomizasyon yöntemi ile çalışmaya dahil edildi. Fosforilkolin kaplamalı EKD sistemleri grup 1'de, kaplamasız EKD sistemleri ise grup 2'de kullanıldı. Koagülasyon faktörlerinin aktivasyon yüzdeleri [faktör (F)-II, F-V, F-VII, F-VIII, F-X, F-XII ve von Willebrand faktör], D-dimer ve antitrombin III düzeyi ameliyat öncesi, sırası ve sonrasında ölçüldü.

Bulgular: Faktör II ve F-X aktivasyon yüzdesi kros-klemp kaldırılmadan hemen önce (T_1) grup 2'de grup 1'e göre anlamlı olarak yüksekti ($p<0.05$). Faktör XII aktivasyon yüzdesi ise ameliyat sonrası (altı saat sonra-T_3 ve bir hafta sonra-T_4) her iki grupta da artmakta idi, ancak bu artış grup 2'de anlamlı olarak daha yüksek bulundu ($p<0.01$). D-Dimer düzeyi her iki grupta da tedricen artarak anlamlı olarak yüksek seyretti ($p<0.001$), ancak gruplar arasında fark gözlenmedi. Antitrombin III aktivitesi her iki grupta da T_1'de başlangıç düzeyine (T_0) göre belirgin olarak azaldı ($p<0.01$). von Willebrand faktör aktivitesi T_1'de ve kardiyopulmoner baypastan (KPB) çıktıktan sonra (T_2) her iki grupta da anlamlı olarak arttı ($p<0.01$); bu iki grup arasında anlamlı bir fark olduğunu göstermedi ($p>0.05$).

Sonuç: Fosforilkolin kaplamalı EKD sistemlere kıyasla, kaplamasız EKD sistemlerinde faktör aktivasyon yüzdesi daha yüksek olmasına rağmen, anlamlı bir klinik farklılığa neden olmamaktadır. Bununla birlikte, hem FK kaplı hem de kaplamasız EKD sistemleri, kardiyopulmoner baypas sırasında benzer biyolojik etkiler sergilemektedir.

Anahtar sözcükler: Kan koagülasyon faktörü; ekstrakorporeal dolaşım; hemakompatibilite; fosforilkolin.

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Extracorporeal circulation (ECC) induces the coagulation-fibrinolysis defect along with a complex systemic inflammatory response and also affects peculiar aspects of the hematological system by significantly contributing to several adverse postoperative complications.[1,2] In recent years, reducing ECC-related adverse events and developing more physiological or hemocompatible ECC materials has taken much effort.[3,4]

Improvements in surface modification and coating techniques with phosphorylcholine (PC) have been used to stop fibrinogen and protein adsorption as well as platelet collection and to inhibit the first step of activation of coagulation, thereby increasing the hemocompatibility of materials such as polytetrafluoroethylene (PTFE), polyethylene, polyurethane, silicone, and polyvinyl chloride (PVC) that are used in ECC circuits.[5] Although the protection of shaped-blood elements, such as neutrophils, platelets, and red blood cells (RBCs) as well as various inflammatory mediators has been well documented with PC-coated ECC, clotting activity factors, which provide hemostasis and coagulation, have not been studied in conjunction with PC-coated ECC and have not been associated with antithrombin III (AT III) or von Willebrand factor (vWF) in the literature.[5-8]

The first aim of the present study was to describe the activity of individual coagulation factors during and after cardiac surgery with cardiopulmonary bypass (CPB) and determine whether they were related to the clotting factors, AT III, and vWF. The second goal was to investigate whether the activity of any other plasma coagulation factor was correlated with clinical implications such as bleeding volume or length of intensive care unit (ICU) stays after cardiac surgery.

PATIENTS AND METHODS

The local ethics committee (22.12.2009/C-020) gave their approval for this study, and we obtained written informed consent from all of the patients. Thirty-three patients with similar demographic characteristics who had been diagnosed with ischemic heart disease (IHD) and were scheduled for elective coronary artery bypass surgery (CABG) were enrolled in the single-blinded study, and the participants were divided into two groups on the basis of odd (group 1) and even (group 2) numbers that were chosen by lot preoperatively. The PC-coated open ECC system was used for the patients in group 1 while the non-coated open ECC system was used for group 2.

Those who had an extremely reduced left ventricular function [ejection fraction (EF) <30%], those who had undergone emergency surgery, reoperations, additional procedures such as valve replacement, carotid endarterectomies, or a left ventricular aneurysmectomies that required hemodialysis during or after the ECC, or those over the age of 80 who did not consent were excluded from the study. In addition, after the study was terminated, five of the patients (three in group 1 and two in group 2) were also excluded because they had used an antiplatelet drug seven days before the operation, which left a total of 28 study participants (24 males, 4 females; mean age 62±12 years; range 41 to 84 years).

The demographic characteristics and postoperative clinical data of the patients is given in Table 1. For the purposes of this study, blood samples were taken at the preoperative (T_0), and perioperative stage just before cross-clamp removal (T_1) as well as after the termination of CPB (T_2) and at the postoperative sixth hour (T_3), and first week (T_4).

The patients were anesthetized by the same physician with midazolam, fentanyl, and vecuronium at appropriate levels for the patients' weight via a standard protocol. No volatile anesthetics were used. Furthermore, the procedures were performed in a normal manner for all of the patients by the same team. Systemic heparin (300 IU/kg) was given at the beginning of the operation and again one hour later to maintain the activated clotting time (ACT) (Hemochron® 801, ITC, Edison, NJ, USA) at above 480 seconds and 200 IU/kg. As in a previous study.[9] 100 IU/kg of additional heparin was administered on an hourly basis as needed.

The PC-coated open ECC system was used for group 1 from the tip of the artery to the tip of the vein end (Compactflo Evo, Sorin Group Italia S.r.l., Milan, Italy) while the non-coated open ECC system (Bıçakçılar-Bıçakçılar Medical Devices Industry and Trade. Co, Istanbul, Turkey) was used applied at the same location for group 2. A cardiotomy return sucker was used for the shed blood in the operation field, and a Stöckert S3 roller pump Sorin Group Deutschland GmbH, München, Germany) was also employed for all of the patients. Mild systemic hypothermia was applied with a nasopharyngeal temperature of 32° C, and hemodilution was achieved with a hematocrit level of 26%. Priming was carried out on all patients using a standard prime volume (1602±202 mL crystalloid prime), and no additional techniques, such as retrograde autologous priming, were needed. The total flow rate was maintained at between 2.2 and 2.4 L/minute with a perfusion pressure of 50-70 mmHg. Myocardial protection was achieved via antegrade cold blood

Table 1. Demographic and preoperative characteristics of the patients in the study

Parameter	Group 1 (n=15)			Group 2 (n=13)			
	n	%	Mean±SD	n	%	Mean±SD	*p**
Age (years)			62 ±12			60±12	0.782
Body surface area (m^2)			1.83±0.17			1.88±0.13	0.416
Gender							
Male	13	84.6		11	84.7		0.644
Diabetes mellitus	4	30.8		3	20.1		0.412
Hypercholesterolemia	8	53.3		7	53.8		0.638
Smoking	10	66.7		9	69.2		0.604
Family history of ischemic heart disease	10	66.7		8	61.5		0.544
Acetylsalicylic acid usage	14	93.3		9	69.2		0.122
Clopidogrel usage	9	60.0		4	30.8		0.122
Statin usage	14	93.3		10	76.9		0.311
Partakers of alcohol	2	15.4		2	15.3		0.644
Ejection fraction			52.9±7.6			49.3±7.8	0.236

SD: Standard deviation; * P values obtained using the Mann-Whitney U test for continuous variables and a chi-square test for categorical variables. A *p*-value of less than 0.05 was considered to be statistically significant.

cardioplegia with potassium, and topical cooling with iced saline and antegrade cardioplegia was repeated every 20 minutes. The effect of the heparin was neutralized with 1 mg protamine for 100 IU.[9]

The patients were followed up by routine hemodynamic monitoring in the cardiovascular surgery intensive care unit (ICU) after the operation, and those with hemoglobin levels of below 10 g/dl along with significant clinical signs, for example hypotension and tachycardia, underwent a blood transfusion during that time.

The blood samples were kept in gel-buffered dry tube, 3.2% sodium citrate and K3 ethylenediaminetetraacetic acid (EDTA) containing tubes. Complete blood counts (CBCs) were analyzed using an fully automated hematology analyzer (ABX Pentra XL 80, Horiba ABX, Inc., Irvine, CA, USA). The blood in the sodium citrate tube was centrifuged for 10 minutes at 5000 rpm, and once plasma was obtained, it was put into 2 ml of Eppendorf cryo for coagulation tests. These were then labeled with the proper encodings and stored for protection in a refrigerator at -80 °C. After all of the samples were collected, heating processes were applied in stages to the frozen plasma samples, and they were measured with a Siemens BCS® XP coagulation measuring device (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany). Next, the AT III plasma activity was measured quantitatively with a Berichrom antithrombin III (A) kit via a chromogenic method (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany), and the D-dimer levels were measured using an INNOVANCE® D-Dimer test kit (Siemens Healthcare Diagnostics Products, GmbH, Marburg, Germany). Furthermore, the factor II (F-II), F-V deficient, F-VIII, F-XI, F-XII, F-VII, and F-X activity percentages were measured with *in vitro* diagnostic F-II, F-V deficient, F-VIII, F-XI, F-XII, F-VII, and F-X reagents (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany) while plasma vWF activity was determined using an *in vitro* platelet agglutination diagnostic Innovance vWF Ac Assay kit (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany).

All analyses were done with the IBM SPSS Statistics version 21.0 for Windows (IBM Corporation, Armonk, NY, USA). The results were expressed as mean and standard deviation (SD) or number and percentage. Comparisons were carried out using the Mann-Whitney U test for non-parametric data and a chi-square test or Fisher's exact test for categorical variables. Group findings at various times were compared with repeated measures of analysis of variance (ANOVA), and in-group comparisons were carried out using the Bonferroni test. A two-sided *p* value of <0.05 was considered to be statistically significant.

RESULTS

The clinical data of the patients is listed in Tables 1 and 2, and we found no significant differences in the demographic, operative, or postoperative parameters. The basal (T_0) measurements of the all of the factors' activation percentages and vWF, D-dimer, and AT III levels were within normal limits and were similar between the two groups (Table 3).

Table 2. Hemostatic parameters in the peri- and postoperative state of coronary artery bypass graft surgery

Parameter	Group 1 (n=15)	Group 2 (n=15)	
	Mean±SD	Mean±SD	*p*
Total heparin administered (IU)	22350±4850	23200±5640	0.223
Protamine administered (gr)	275.34±21.23	298±24.52	0.863
Total distal anastomosis	3.69±0.51	3.47±0.83	0.479
Total surgery time (minutes)	370±46	370±84	0.946
Cardiopulmonary bypass time (minutes)	118±23	113±20	0.741
Aortic cross-clamp time (minutes)	59±16	67±15	0.157
Length of intensive care unit stay (hours)	90.35±16.32	70.43±21.02	0.241
Intubation time (hours)	21.11±2.82	16.85±8.15	0.153
Transfused erythrocyte suspension (Unit)	1.12±0.67	2.01±0.92	0.534
Transfused fresh frozen plasma (Unit)	1.75±0.94	1.63±0.69	0.753
Total blood loss (cc)	1177±645	1235±456	0.856
Mortality (%)	0	0	

SD: Standard deviation; * P values obtained using the Mann-Whitney U test for continuous variables. A p-value of less than 0.05 was considered to be statistically significant.

The patients were extubated shortly after the completion of the operation, and no surgical complications, such as reoperations due to bleeding, thromboembolic events, myocardial infarction (MI), lengthened stays on the ICU or hospital, or mortality were reported during the study (Table 2). The administered doses of heparin and protamine are given in Table 2, and the ACT values are shown in Table 3, and no significant differences were noted between the two groups.

The analysis of the factors' activation percentages is shown in Table 3. All of the measured parameters differed significantly from the T_0 when the in-group comparison was conducted ($p<0.0001$). The F-II and F-X activity percentages were also significantly different, with the measured value being reported as "no coagulation" between the groups at T_1 (0 vs. 6.5±5.8 and 0 vs. 13.7±6.5, respectively; $p<0.05$). Additionally, the F-XII activity percentage in group 2 was significantly higher than in group 1 at T_3 and T_4 (134.2±41.4 vs. 171.3±39.5 and 165.4±20.2 vs. 185.2±36.2, respectively; $p<0.05$).

However, the AT III values did not differ significantly between the two groups. There were decreased levels within the group comparison, and a statistically significant reduction of under 80 mg/dl was seen at T_1 and T_2 compared with the T_0 levels (Table 3).

Although there was no marked difference in the D-dimer values between the groups, they were exponentially higher at T_1, T_2, T_3, and T_4 within the groups (Table 3).

Moreover, the vWF activity percentage was significantly high at T_1 compared with T_0, but the difference was not significant between the groups (Table 3).

DISCUSSION

Our research revealed a significant variation in the plasma activity of F-II and F-X during CPB and F-XII after CPB. Weerasinghe and Taylor[10] reported that constant contact was present between the shaped elements of the blood and the surface of the ECC during CPB as well as the continuous activation of factors and consumption of platelets by the blood sucked from the non-endothelial surgical field, all of which were important causes of morbidity and mortality in the cardiac surgery postoperative period.

Coating the ECC with PC promises a reduction in thrombogenicity. Ishihara et al.[6] defined this antithrombogenicity as a reduction in adhesion molecules on the surfaces coated with PC which provides a natural zwetterionic structure as well as red blood cells and forms a biomembrane-like (biomimicry) layer of the material' surface. This layer interacts with the blood cell components and proteins minimally. In our study, the F-II and F-X activation percentages were elevated in group 2 at T_1 in spite of the presence of heparinization. This suggests that F-II, a key player in the coagulation process, and F-X, which is commonly seen on the pathway of clotting, were overactivated. De Somer et al.[5] showed that immediately after the start of CPB, the thromboxane B2 (TXB-2) (a potent thrombocyte activator and aggregator) blood concentration fell quickly, after temporarily rising

Table 3. The mean values of the activity percentage of the factors and the vWF, D-dimer, and AT III levels at specified times

Parameters	T_0	T_1	T_2	T_3	T_4	*p***
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Factor II activity %						
G I (n=15)	90.4±16.1	0‡*	46.5±24.8§	88.7±15.6	131.6±16.8†*	<0.0001
G II (n=13)	93.6±24.9	6.5±5.8‡*	27.3±31.2§	84.5±17.6	113.7±24.6*	<0.0001
Factor V activity %						
G I (n=15)	92.3±21.9	20.3±14.7‡	49.1±21.5	90.3±7.6	132.7±28.9†	<0.0001
G II (n=13)	95.3±15.2	14.4±11.4‡	61.2±19.1§	83.5±13.6	136.2±27.3	<0.0001
Factor VII activity %						
G I (n=15)	74.2±12.0	12.8±5.9‡	39.6±20.9§	72.4±25.8	77.0±3.4	<0.0001
G II (n=13)	81.7±10.9	15.8±5.6‡	39.2±21.1§	86.6±11.7	92.1±12.5	<0.0001
Factor VIII activity %						
G I (n=15)	111.3±23.5	0‡	78.8±16.9§	134.1±32.1	179.7±27.7†	<0.0001
G II (n=13)	114.8±17.2	0‡	78.7±28.7§	136.9±31.2	165.2±32.1†	<0.0001
Factor X activity %						
G I (n=15)	94.5±14.7	0‡*	48.7±17.7§	82.3±16.0	131.1±50.6†	<0.0001
G II (n=13)	93.2±15.1	13.7±6.5‡*	38.5±23.6§	91.9±16.2	132.5±42.3†	<0.0001
Factor XII activity %						
G I (n=15)	81.0±14.2	0‡	30.1±12.8§	134.2±41.4¶*	165.4±20.2†*	<0.0001
G II (n=13)	74.5±10.6	0‡	27.2±9.5§	171.3±39.5¶*	185.2±36.2†*	<0.0001
ACT (second)						
G I (n=15)	121±28	706±250‡	696±322§	122±22	112±8	<0.0001
G II (n=13)	124±24	689±340‡	592±243§	124±28	131±13	<0.0001
D-dimer (mg/L FEU)						
G I (n=15)	0.42±0.3	6.38±1.3‡	4.14±0.7§	13.34±8.5¶	14.86±6.3†	<0.0001
G II (n=13)	0.44±0.2	7.50±6.8‡	4.05±0.9§	12.01±6.4¶	13.43±4.7†	<0.0001
AT III activity %						
G I (n=15)	86.3±11.5	65.7±12.7‡	65.5±11.0§	86.6±12.4	90.8±9.4	<0.0001
G II (n=13)	92.8±14.7	72.3±10.1‡	70.9±11.6§	80.5±10.1	85.2±7.8	<0.0001
vWF activity %						
G I (n=15)	64.7±15.3	88.4±25.4‡	109.5±30.1§	93.7±19.8¶	86.3±12.1†	<0.0001
G II (n=13)	71.2±21.7	104.7±30.8‡	113.1±29.6§	104.1±26.3¶	91.8±11.5†	<0.0001

T_0: Preoperative; T_1: Perioperative just before cross-clamp removal; T_2: Perioperative after termination of CPB; T_3: Postoperative sixth hour; T_4: Postoperative first week; SD: Standard deviation; G: Group; ACT: Activated clotting time; FEU: Fibrinogen equivalent unit; AT III: Antithrombin III; vWF; von Willebrand Factor; * Indicates between group comparisons using the Mann-Whitney U test. A *p*-value of less than 0.05 was considered to be statistically significant; ** *P* values obtained using repeated measures of analysis of variance (ANOVA). In-group comparisons were carried out using the Bonferroni test. Superscripts were indicated as the following "‡: T_0-T_1; §: T_0-T_2, ¶: T_0-T_3; †: T_0-T_4". All the *p* values of the superscripts' were less than 0.01 and were considered to be statistically significant. Continuous data was expressed as mean ± standard deviation (SD). The measured values of the activity percentage of the factors that is shown as "0" in the table was reported as "no coagulation".

in the beginning, with the use of PC-coated ECC systems. In contrast, they found that the TXB-2 blood concentration began to rise and remained at a high plateau until the end of CPB with the non-coated ECC group. One possible interpretation of their findings is that the bio-compatible PC-coated surface that causes the activation of platelets was rapidly made passive.[11] In our study, the difference in the F-II and F-X activation percentages between the groups at T_1 were consistent with the findings of the De Somer et al.[5] study. Similarly, the adsorption of fibrinogen and platelets was shown to be inhibited by PCC in an in vitro study by Campbell et al.[8] We determined that despite the quick rise in F-XII activation percentage, it was almost the same in both of our groups at the time of CPB output. Furthermore, the rising curve in F-XII activation percentage in group 2 that we discovered may have been due to the differences in the surface. Li et al.[7] showed that the surface of PC-coated systems resisted adsorption of F-XII and delayed the initiation of coagulation by the intrinsic pathway, and their results were similar to ours.

We also determined that the plasma activity of AT III decreased below the 80% level. Heparin

activity occurs by connecting heparin to the AT III on a specific pentasaccharide sequence, which primarily leads to the inactivation of coagulation factors such as F-IIa and F-Xa.[12] Although we found that the ACT values were adequate for CPB, the AT III levels were under 80 U/dl in the blood samples at T_1 and T_2, and these low levels might have caused the continuous subclinical coagulation in our study. In fact, Despotis et al.[13] highlighted that low AT III levels, particularly when they are under 80 U/dL, may be inadequate for anticoagulation.[13]

Finally, we identified a marked increase in the vWF levels during CPB as well as a gradual increase in the D-dimer levels during CPB and after the surgery. Cardiopulmonary bypass-associated fibrinolysis frequently emerges after a rapid rise in D-dimer levels after neutralizing the effect of heparin.[14] Like the study by Páramo et al.[15] the D-dimer levels in our groups increased significantly during CPB and reached their peak after the administration of protamine.

Successful hemacompability during CPB offers increased protection in the hemostasis process via a reduction in consumption, less coagulation and the activation of coagulation factors, and expected low D-dimer values.[16] We determined that the D-dimer levels were the same in both of our groups, and after the surgery, they showed similar gradually increasing rising curve until postoperative week one. This similarity may indicate that the patients' burden of fibrinolysis may also have been similar. As Nisanoğlu et al.[17] pointed out in their study, when increased hemacompability, subclinical thrombosis and fibrinolysis continue a rise in D-dimer levels usually occurs. The primary source of vWF is the vascular endothelium, which produces it without stimuli and also provides the rapid release of intracellular stores in response to other stimuli like thrombin, fibrin, and vasopressin. Wittwer et al.[18] have found that increase plasma vWF levels after surgery involving CPB. During CPB, many different variables, particularly vascular endothelial injuries, can influence vWF levels. In addition, endothelial cells can be damaged by both particles of reactive oxygen species (ROS) during CPB and free radicals during reperfusion caused by the effect of activated platelets.[19] Holdright et al.[20] mentioned that the vWF antigen (vWF:Ag) levels during the induction of anesthesia decrease before the introduction of cross-clamping due to hemodilution secondary to a decrease in hematocrit levels. However, they found that after the cross-clamping, the levels continued to climb to the levels seen at induction, and they reached their highest levels when the CPB was terminated. They also determined that the rise in the vWF levels after the removal of the aortic cross-clamp were associated with vascular endothelial damage and the reperfusion of coronary arteries. Their findings were consistent with ours, and we did not identify any significant differences in the vWF levels between the groups.

Conclusion

Our study results showed that PC-coated ECC systems were not superior to non-coated ECC systems. In spite of the fact that there were differences at some of the time points, by using the same CPB technique and the activation percentages of the factors, our two groups of patients who underwent cardiac surgery had similar biological effects.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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