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Antithrombotic properties of hemofilter coated with polymer having a hydrophilic blood-contacting layer

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Abstract

Objective: Extracorporeal circulation devices are coated with a biocompatible polymer coating agent (BPCA) that has a hydrophilic blood-contacting layer, but hemofilters are not. We aimed to investigate the antithrombotic properties of a BPCA-coated hemofilter.

Methods: Four experiments using BPCA-coated circuits and non-coated hemofilters and four experiments using BPCA-coated circuits and BPCA-coated hemofilters were performed with whole human blood and compared by measuring the circuit pressure every 5 min, antithrombin activity every 40 min, and thrombin–antithrombin complex every 40 min, for a total of 240 min of recirculation.

Results: The mean time required for the pressure at the inlet of the hemofilter to increase sharply was longer in BPCA-coated than in non-coated hemofilters (66 ± 11 min vs 25 ± 9 min, $p < 0.01$). The mean antithrombin activity value at 200 and 240 min of recirculation was significantly higher in the experiments with BPCA-coated versus non-coated hemofilters (43.3 ± 2.87 vs 33.3 ± 5.74, $p = 0.04$; 42.8 ± 3.59 vs 31.0 ± 5.35, $p = 0.01$, respectively); the antithrombin activity values at the other time points were not significantly different. Furthermore, all thrombin–antithrombin complex values in experiments with the BPCA-coated hemofilters achieved overrange at 80 min of recirculation, whereas those with the non-coated hemofilter achieved overrange at 40 min.

Conclusion: This study suggests that BPCA-coated hemofilters can inhibit antithrombin consumption, contributing to antithrombotic effects in extracorporeal circulation circuits.

Keywords

Antithrombin, cardiopulmonary bypass, dialysis, hemofilter, polymer, thrombin–antithrombin complex

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Introduction

Currently, in the field of cardiopulmonary bypass surgery, the foreign surfaces of extracorporeal circulation circuit devices, such as polyvinyl chloride tubes, hard-shell reservoirs, and oxygen membranes, are coated with a biocompatible polymer coating agent (BPCA) to reduce thrombogenicity.[1–3] BPCA is composed of a hydrophobic backbone that adheres to circuit surfaces and a hydrophilic blood-contacting layer. The hydrophilic layer swells upon contact with blood, creating a water-filled boundary layer that maintains protein conformation and prevents surface activation.[4] Without this coating, the blood is exposed to the circuit surface, activating the coagulation cascade. Although most devices in the cardiopulmonary bypass circuit are coated with BPCA, the hemofilter, which is used

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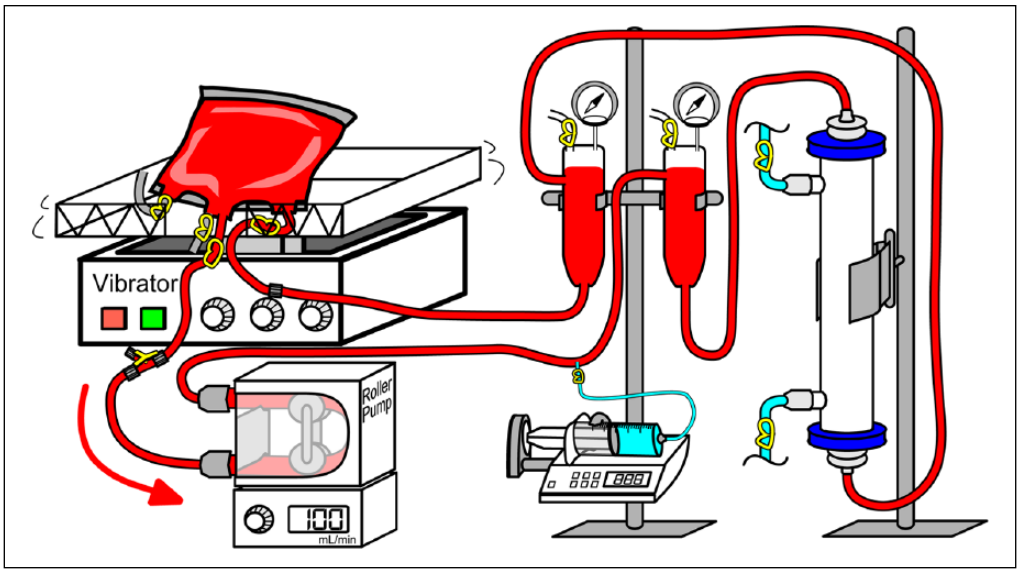

Figure 1. Experimental circuit. Human blood was collected in a soft bag reservoir, vibrated on the vibrator, and circulated with a roller pump. Two chambers were configured at the inlet and outlet pathways of the hemofilter to measure each pathway's pressure. A line for protamine administration was positioned at the pathway before the inlet chamber, and protamine was administered by infusion pump. A sampling port was positioned at the pathway before the roller pump.

for blood concentration or blood filtration, is not coated with BPCA.

Hemofilters are made of more than 10,000 hollow fibers consisting of a polymer membrane. The polymer membrane has side pores through which molecules can pass. The pore size is important for proper filtration performance; only molecules smaller than the pore can pass, maintaining the concentrations of molecules larger than the pore. For example, one type of hemofilter, the high-flux membrane, is widely used in hemofiltration; this filter has <0.01 and $\geqslant 0.6$ sieving coefficients for albumin and beta-2-microglobulin, respectively.[5] Thus, albumin can only minimally pass, but beta-2-microglobulin can more readily pass through the membrane pores. Considering the principle of filtration, BPCA coating might be unsuitable in hemofilters because of the potential for the coating agent to expand on the membrane surface, narrowing the pore diameter.

If a BPCA-coated hemofilter could be used, favorable effects could be expected in terms of anticoagulation of the extracorporeal circulation, not only in cardiopulmonary bypass surgeries but also in hemodialysis treatment. In a patient undergoing hemodialysis, the blood is exposed to the hemofilter three times a week for 4–5 h per session;[6,7] therefore, antithrombotic properties are required.

To clarify the features of BPCA-coated hemofilters, we previously performed experiments to confirm that the BPCA coating did not disturb functions of diffusion and filtration and found that there is no malfunction of filtration and diffusion in BPCA-coated hemofilters.[8,9] Therefore, further investigation of BPCA-coated hemofilters to evaluate the antithrombotic effects is justified.

In this study, we aim to examine the anticoagulation effects of BPCA-coated hemofilters in contact with whole human blood using in vitro experiments.

Methods

In vitro experiments were performed to compare circuit pressures and blood coagulation markers in blood exposed to BPCA-coated and non-coated hemofilters at similar exposure durations.

Materials

The BPCA product (SEC-1™; Toyobo, Osaka, Japan) used in this study was a copolymer composed of hydrophobic alkyl acrylate, hydrophilic polyethylene glycol acrylate, and water-repellent silicone methacrylate. The coating procedure involved spreading the BPCA layer using a solvent.

Eight columns consisting of polyethersulfone membrane (Hemocrystal; MERA, Tokyo, Japan), which had the same lot number, were employed as hemofilters in this study. Hemocrystals had 1.1 m^2 membranes and are considered high-flux membranes; the sieving coefficients of beta-2-microglobulin and albumin were 0.6 and $\leqslant 0.01$, respectively.[10]

An experimental circuit was configured consisting of a soft bag reservoir, polyvinyl chloride tubes, chambers, and a hemofilter and was installed with a roller pump, an infusion pump, and two digital manometers, which can measure pressure up to 500 mmHg (Figure 1). Four experimental circuits coated with BPCA on the foreign surfaces of the circuit configurations including the hemofilter ($PC_{1,2,3,4}$)

were prepared, and four experimental circuits coated with BPCA on the foreign surfaces of the circuit configurations excluding the hemofilter ($NC_{1,2,3,4}$) were also prepared. Those devices were coated with BPCA using the solvent infiltration method.

To evaluate the anticoagulation effects precisely, whole human blood was used. We recruited healthy volunteers, who each provided 200 mL of whole blood. A healthy volunteer was defined as having a hemoglobin (HGB) concentration >13.5 g/dL, with no medical events within the prior 1 month, no transfusion history, and no current disease diagnosis. The ethic committees of the National Hospital Organization Kure Medical Center approved this study protocol, and written informed consent was obtained from each volunteer.

Procedures

For blood collection, a soft bag reservoir was prepared and 3000 units of unfractionated heparin were added to the reservoir. The blood was added to the soft bag reservoir using a 17-gauge needle, and the reservoir was continually shaken thoroughly in the vibrator during the test. Upon collecting 200 mL of blood, the soft bag reservoir was disconnected from the needle and was connected to the experimental circuit, which was primed with saline. The hemofilter was filled with primed saline, filling both the inside and the outside of the membrane. The blood was recirculated at 300 mL/min with a roller pump to mix the blood with pre-primed saline in the circuit. After 3 min, 15 mg/min of protamine was administered to the circuit to reverse the heparinization. When 50 mg of total protamine was administered, administration was stopped. After 3 min, 6 mL of blood was sampled at the sampling port to evaluate baseline coagulation markers. Subsequently, the blood recirculation rate was changed from 300 to 100 mL/min, and the blood was continually recirculated for 240 min. The pressures at the inlet and outlet chambers were measured every 5 min. An amount of 6 mL of blood was sampled every 40 min to measure coagulation markers.

To compare BPCA-coated versus non-coated hemofilters, similar experiments were performed with four circuits using a BPCA-coated hemofilter and four circuits using a non-coated hemofilter. All experiments were performed in a room maintained at a temperature of 38°C.

The sampled blood was used to measure HGB, prothrombin time of international normalized ratio (PT-INR), antithrombin activity (ATA), and thrombin–antithrombin complex (TAT). HGB was measured using a hematology analyzer (KX-21; Sysmex, Hyogo, Japan). For PT-INR, the transmitted light detection method (HemosIL RecombiPlas Tin; Instrumentation Laboratory Company, Bedford, MA, USA) was used. For ATA, the synthetic substrate method (HemosIL Antithrombin; Instrumentation Laboratory Company) was used. For TAT, the chemiluminescent enzyme immunoassay (STACIA CLEIA TAT; LSI Medience Corp., Tokyo, Japan) was used; the upper limit of detection for this assay was 120 ng/mL.

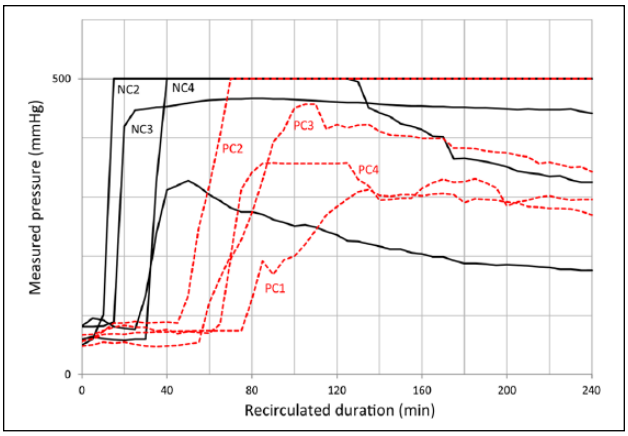

Figure 2. Pressures at the inlet chamber correlated with blood recirculation duration. Red dotted lines indicate pressure transition every 5 min at the inlet chamber in the experiments with biocompatible polymer (BPCA)-coated hemofilters; black solid lines indicate the values with non-coated hemofilters. The horizontal axis indicates the recirculated duration, and the vertical axis indicates the measured pressure values (mmHg). Because the digital manometer cannot measure values >500 mmHg, values >500 mmHg were plotted at a value of 500 mmHg. NC_n: experimental number for the non-coated hemofilter; PC_n: experimental number for the BPCA-coated hemofilter.

Statistical analysis

Continuous variables were compared using Student's *t*-test performed using MS Excel software (Microsoft Corp., Redmond, WA, USA). The significance level was set at $\alpha = 0.05$.

Results

The measured pressures at the inlet chambers in BPCA-coated and non-coated hemofilters were plotted and joined, as shown in Figure 2. The mean time (n = 4) when the pressure rose sharply, defined as the point when pressure increased >50 mmHg in 5 min, was longer in BPCA-coated than in non-coated hemofilters (66 ± 11 min vs 25 ± 9 min, $p < 0.01$). All measured pressure values at the outlet chambers in each experiment were <60 mmHg.

Table 1 reports the coagulation markers measured every 40 min in each experiment. The ATA and TAT values according to recirculated duration are shown in Figures 3 and 4, respectively. The ATA mean value (n = 4) at 200 and 240 min of recirculation was significantly higher in the experiments with BPCA-coated compared with non-coated hemofilters (43.3 ± 2.87 vs 33.3 ± 5.74, $p = 0.04$; 42.8 ± 3.59 vs 31.0 ± 5.35, $p = 0.01$), whereas

Table 1. Measured values in each circulated duration.

Experiment	Measurement	Circulated duration (min)						
		0	40	80	120	160	200	240
PC_1	HGB (g/dL)	9.8	9.9	10.1	10.2	10.3	10	9.9
	PT-INR	1.94	2.09	2.18	N/A	N/A	N/A	N/A
	ATA (%)	52	50	49	45	41	43	41
	TAT (ng/mL)	1.2	14.4	>120	>120	>120	>120	>120
PC_2	HGB	8.6	9.3	8.7	8.7	8.7	8.7	8.7
	PT-INR	1.83	1.78	N/A	N/A	N/A	N/A	N/A
	ATA	55	56	47	45	46	47	48
	TAT	1.4	24.8	>120	>120	>120	>120	>120
PC_3	HGB	7.8	8.3	7.3	7.4	7.5	7.5	7.6
	PT-INR	2.11	2.03	N/A	N/A	N/A	N/A	N/A
	ATA	50	54	44	40	39	40	40
	TAT	<1.0	8.1	>120	>120	>120	>120	>120
PC_4	HGB	8.2	8.4	7.7	7.8	7.9	7.9	7.8
	PT-INR	2.24	2.44	N/A	N/A	N/A	N/A	N/A
	ATA	50	47	38	35	37	43	42
	TAT	<1.0	9.2	>120	>120	>120	>120	>120
NC_1	HGB	8.4	8.3	8.3	8.3	8.2	8.2	8.3
	PT-INR	2.15	N/A	N/A	N/A	N/A	N/A	N/A
	ATA	42	38	37	33	33	34	34
	TAT	1.1	>120	>120	>120	>120	>120	>120
NC_2	HGB	9	8.6	8.6	8.6	8.5	8.6	8.6
	PT-INR	1.99	N/A	N/A	N/A	N/A	N/A	N/A
	ATA	47	33	26	25	23	25	23
	TAT	82.5	>120	>120	>120	>120	>120	>120
NC_3	HGB	8.3	8.5	8.3	8.2	8.2	8.2	8.2
	PT-INR	1.85	N/A	N/A	N/A	N/A	N/A	N/A
	ATA	52	50	41	35	37	36	34
	TAT	1.5	>120	>120	>120	>120	>120	>120
NC_4	HGB	7.2	6.9	7.3	7.2	7.2	7.1	7.1
	PT-INR	2.30	N/A	N/A	N/A	N/A	N/A	N/A
	ATA	42	41	38	39	36	38	33
	TAT	<1.0	>120	>120	>120	>120	>120	>120

PC_n: number of experiments with polymer-coated hemofilter; NC_n: number of experiments with non-coated hemofilter; HGB: hemoglobin; PT-INR: prothrombin time of international normalized ratio; ATA: antithrombin activity; TAT: thrombin–antithrombin complex; N/A: not applicable.

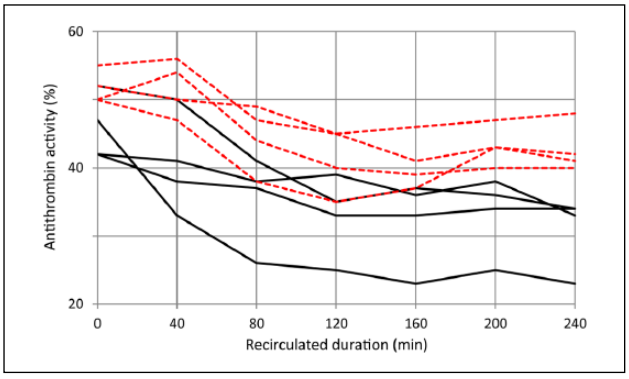

Figure 3. Measured values of antithrombin activity (ATA) every 40 min of blood recirculation. Red dotted lines indicate ATA transition every 40 min of recirculation in the experiments with biocompatible polymer–coated hemofilters; black solid lines indicate those with non-coated hemofilters. The horizontal axis indicates recirculated duration, and the vertical axis indicates ATA (%).

the values at other time points were not significantly different. The TAT values in experiments with the BPCA-coated hemofilters were over the limit of detection at 80 min of recirculation; with the non-coated hemofilters, TAT values were over the limit of detection at 40 min.

Discussion

Many reports have been published regarding the biocompatibility of BPCA-coated medical equipment.[11–13] The results of this study confirm the beneficial effect, in terms of anticoagulation, of the BPCA-coated hemofilter.

The pressure measurements suggest that the time required before the initiation of coagulation is significantly later in the circuits with BPCA-coated hemofilters compared with non-coated hemofilters. Because surfaces that contacted blood in each experimental circuit were all coated with BPCA, with the exception of the hemofilter, the only difference in the two experimental groups was the presence

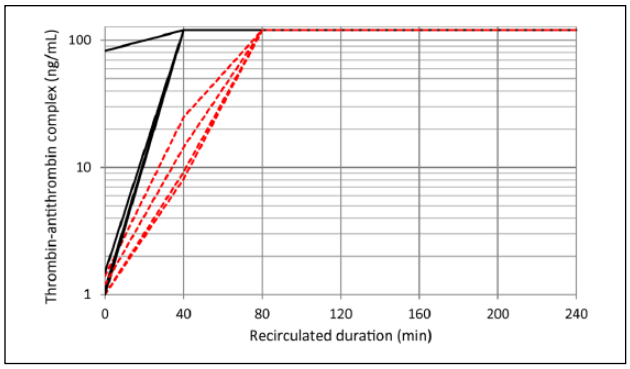

Figure 4. Measured values of the thrombin–antithrombin complex (TAT) every 40 min of blood recirculation. Red dotted lines indicate TAT transition every 40 min of recirculation in the experiments with biocompatible polymer–coated hemofilters; black solid lines indicate those with non-coated hemofilters. The horizontal axis indicates recirculated duration, and the vertical axis, which is reproduced to a logarithmic axis, indicates TAT (ng/mL). Because the upper limit of detection for TAT was 120 ng/mL, values >120 ng/mL were plotted at a value of 120 ng/mL.

or absence of BPCA coating on the hemofilters. Thus, Figure 2 clearly shows the coagulation-resistant properties of the BPCA-coated hemofilter. Furthermore, TAT transition, shown in Figure 4, shows that the coagulation trend was similar to the pressure transition. TAT, an equimolar complex formed by thrombin and antithrombin, resulting in thrombin inactivation,[14,15] is well recognized as a sensitive parameter of activated coagulation in circulating blood.[16,17] TAT transition results also suggest that BPCA coating can reduce the activation of the coagulation cascade. Interestingly, at 40 min of recirculation in BPCA-coated hemofilters, TAT values increased, but the pressure transition remained plateaued. This finding suggests that TAT accelerates before generating the coagulation cascade, confirming the general theory that TAT is a sensitive parameter of coagulation activation.

The results of pressure analysis and TAT show trends in the anticoagulation effects of BPCA-coated hemofilters during the early phase of recirculation, but these results do not clarify the effects during long-term recirculation. However, the results of ATA might reflect the anticoagulation properties of BPCA-coated hemofilters during long-term recirculation. Antithrombin is an important physiological anticoagulant that can inhibit a wide range of coagulation factors, including thrombin and others.[18] Therefore, thrombin generation results in antithrombin consumption, leading to decrement in ATA.[19] In this study, a significant decrement in ATA was shown over a longer time period with the non-coated hemofilters than with the BPCA-coated hemofilters, indicating that the BPCA coating can inhibit antithrombin consumption slowly and continually; however, this positive effect cannot be demonstrated during short-term exposure.

Considering the cardiopulmonary bypass circuit, the BPCA-coated hemofilter is valuable. Because a hemofilter is mainly used for concentration of blood, due to its filtration functions, blood circulates into a hemofilter over a prolonged duration during extracorporeal circulation.[20] Furthermore, a hemofilter is used for various perfusion techniques such as modified ultrafiltration,[21] dilutional ultrafiltration,[22] zero-balance ultrafiltration,[23] or any other hemopurification method.[24,25] These techniques also require blood circulation into a hemofilter for prolonged duration. Considering that the BPCA-coated hemofilter reduces antithrombin consumption, it could produce beneficial effects during the post-extracorporeal circulation phase. Postoperative ATA has been reported to be associated with major adverse cardiac events, regardless of preoperative ATA.[26] Furthermore, post-extracorporeal circulation ATA inversely correlates with the need for transfusion or the development of acute renal failure.[27] Therefore, the BPCA-coated hemofilter, which can preserve ATA, could lead to reduced mortality in cardiopulmonary bypass surgeries. Furthermore, there are many reports concerning the favorable effects of BPCAs on the reduction of cell adhesion, hemolysis, protein adhesion, and inflammatory markers.[11–13,28,29] Another advantage of the BPCA-coated hemofilter is its biocompatibility, which could help improve the prognosis of patients undergoing extracorporeal circulation.

Regarding hemodialysis, the BPCA-coated hemofilter is also valuable, in particular, for successful treatment of patients with acute kidney injury. Acute kidney injury is a systemic inflammatory condition, and its inflammatory response can trigger the activation of both the intrinsic and extrinsic coagulation cascades,[30] inducing thromboembolism in the extracorporeal circuit regardless of heparinization.[31,32] Therefore, preservation of antithrombin levels might enhance the longevity of the extracorporeal circuit in patients requiring continuous renal replacement therapy.[32,33] Furthermore, as many centers practice anticoagulant-free hemodialysis for patients at high risk of bleeding, heparin-coated hemofilters have recently been introduced into clinical practice.[34,35] However, reduction in thrombogenicity has been uncertain.[36,37] The pressure graph in this study also suggests that it would be difficult to perform anticoagulant-free hemodialysis with the BPCA-coated hemofilter. However, because the antithrombotic advantages of this filter were clearly confirmed in this study, continuing investigation is warranted.

A similar examination of BPCA-coated membranes has been published,[38] but it was performed using a minimized filter and bovine blood. In this study, experiments were performed with human blood and used a hemofilter consisting of an aggregate of membranes, thus mimicking the clinical setting, which is an important point. However, a major limitation of this study is that only eight experiments were performed; therefore, future studies with a

higher number of experiments are required to confirm our findings.

Conclusion

The results of this study show that the BPCA-coated hemofilter can delay circuit thrombogenicity and inhibit antithrombin consumption compared with the non-coated hemofilter. This preliminary study suggests that a BPCA-coated hemofilter is superior in terms of antithrombotic properties.

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Declaration of conflicting interests

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