RESEARCH

Effects of hydrophilic polymer-embedded membrane on permeability and cell adhesion during continuous hemofiltration

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Abstract

Background and Aims: Clotting within the membrane and/or venous 'air trap' chamber is common problems during continuous blood purification therapy. Frequent clotting during continuous blood purification therapy leads to inadequate solute removal, an increased circuit and filter cost, and an increased burden for the medical staff. Improvements in filter membrane materials may reduce the extent of clotting and prolong the filter life. The purpose of the present study was to clarify the characteristics of an NV polymer-embedded membrane (NV-PS) after long-term use, especially the adhesiveness of blood cells and changes in the solute removal performance.

Methods: Continuous hemofiltration (CHF) experiments using a permeate recycle mode were performed for 24 h using the same porcine whole blood divided into two portions to compare the NV-PS with a conventional polysulfone membrane (PS). The activated clotting time was adjusted to within a range of 300–400 s. The change in the dextran sieving coefficient (SC) of the membrane and the residual blood clots in the filters were evaluated after the completion of the CHF experiment.

Results: The increase in the transmembrane pressure and the pressure drop of the hemofilter were significantly smaller using the NV-PS than with the PS. For larger molecules (SC $\leqq$ 0.4), the reduction in SC after blood contact was significantly smaller for the NV-PS. Fewer blood cells remained in the residual blood clots when the NV-PS was used.

Conclusion: NV-PS has the advantages of showing a lower degree of reduction of the solute removal performance and also a lower degree of clogging of the hollow fibers during prolonged circulation. These characteristics may be expected to be advantageous when this membrane is used for continuous blood purification therapy in acute-phase patients.

Keywords: Continuous blood purification therapy, NV polymer, Filter life, Residual blood clots, Molecular weight cutoff curve

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Introduction

Continuous blood purification therapy (CBP) is a well-accepted treatment modality for acute renal failure in the field of intensive care [1–3]. However, clotting within the membrane and/or venous 'air trap' chamber is a common problem [4, 5] during CBP treatment, since the hemofilter causes the activation of platelets and the coagulation cascade as blood passes through the filter. Frequent

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clotting during CBP leads to inadequate solute removal, increased circuit and filter costs, and lost time for the medical staff [6]. Several methods have been used to prevent hemofilter clotting and maintain circuit patency, such as precoating the circuit with heparin [7], using a higher blood flow rate [8], using a pre-dilution technique [9, 10], and regional cooling of the extracorporeal blood circuit [11]. Improvements in filter membrane materials may also reduce the extent of clotting and prolong filter life.

Recently, a membrane consisting of a hydrophilic NV polymer on a polysulfone membrane has been used for maintenance hemodialysis therapy. In an in vitro experiment, the membrane characteristics of the NV polymer-embedded membrane reportedly included increased hydrophilicity on the surface, less adsorption of von Willebrand factor and fibrinogen, less platelet adhesion on the membrane surface, and less leukocyte activation [12]. In other in vitro experiments, NV polymer-embedded membrane was also reported to reduce the direct interaction inducing platelet activation and neutrophil activation [13] and the formation of platelet-neutrophil complexes induced by membrane contact [14]. Increased biocompatibility in a clinical study was also reported, including less adhesion of platelets [15], less production of interleukin-6, and improved resistance to erythropoietin stimulating agent [16] and the endothelial function [17] of maintenance dialysis patients. Especially, the anticoagulation properties of NV polymer-embedded membranes might be beneficial in CBP by reducing the extent of clotting and prolonging the filter life, compared with conventional hemofilters.

Since the tendency for coagulation and platelet activation differs for each patient receiving CBP depending on the patient's clinical condition, a clinical comparison of hemofilter lifetimes is difficult. Therefore, obtaining useful information to develop or modify the membrane materials is also difficult. An in vitro extracorporeal system can be used to resolve this difficulty, enabling parameters such as the reduction in solute removal performance, the lifetime of the hemofilter, blood clotting, and platelet activation to be evaluated. We previously evaluated the adhesiveness of blood cells and the change in solute removal performance of modified polysulfone hemofilters with an increased polyvinylpyrrolidone (PVP) coverage over the surface of the membrane by comparing them with a conventional polysulfone hemofilter [18] using an in vitro extracorporeal system as a 24-h in vitro continuous hemofiltration (CHF) experimental model [19]. With this in vitro circulation model, however, the protein concentration and some coagulation factors decreased with time, and the activation of the cascade initiated by factor XII, which is usually started

by the interaction between the blood and the membrane material, was suppressed by nafamostat mesilate; consequently, we could not sufficiently evaluate the interaction between the blood and the hemofilter material.

The purpose of the present study was to clarify the characteristics of the NV polymer-embedded membrane for long-time use, especially the adhesiveness of blood cells, which affects the lifetime of the hemofilter, as well as the change in solute removal performance, by comparing an NV polymer-embedded polysulfone membrane with a polysulfone membrane with an increased PVP coverage. To this end, we modified the in vitro hemofilter evaluation system that we had previously developed for CHF [19] by changing the anticoagulant and the dose control for anticoagulation. The CHF experiments were performed for 24 h using the same porcine whole blood sample divided into two portions to compare the two types of hemofilter. The change in water permeability and the dextran sieving coefficient (SC) of the membrane and the blood cell adhesion on the membrane after CHF were evaluated.

Materials and methods

Hemofilter

Two types of hemofilters were evaluated in a 24-h in vitro CHF experiment; a polysulfone membrane hemofilter with an increased PVP coverage (Hemofeel® SHG; Toray Medical, Tokyo, Japan, hereinafter, simply PS), a hydrophilic polymer (NV polymer)-embedded polysulfone membrane hemofilter (Hemofeel® SNV; Toray Medical, Tokyo, Japan, hereinafter, simply NV-PS). The membrane area of each hemofilter was 1.0 m², and the length and diameter of the housing were the same.

Blood preparation

Fresh porcine blood was obtained from a dealer of animal blood and organs for research use (Tokyo Shibaura Zouki, Tokyo Japan) on the morning of the day of the experiment. After collecting blood from the animal, sodium citrate was immediately added (final concentration: 10 mM). The blood was carefully transferred in a cooling box to our laboratory.

Penicillin and streptomycin (15140-122; GIBCO, Grand Island, NY) were added to the blood to final concentrations of 100 units/mL and 100 µg/mL, respectively. Then, porcine blood was dispensed into 14 individual 1.5-mL tubes. Calcium chloride solution (1 M) was added in 0.5 µL increments to each of the dispensed porcine blood samples to create a dilution series with a final calcium chloride concentration of 0 to 6.5 mM. After 30 min of shaking at 37 °C, the activated clotting time (ACT) was measured using a microcoagulator (Hemochron Signature Elite; Accriva Diagnostics, Inc., CA, USA) to

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determine the amount of calcium chloride that should be added to adjust the ACT to 300–400 s. After adding heparin (300 units/L) and an appropriate amount of calcium chloride to the remaining porcine blood to be used in the CHF experiment, the ACT was measured once again to confirm that it was within a range of 300–400 s; if the ACT did not fall within this range, the ACT was readjusted by adding trisodium citrate or calcium chloride.

Procedure for CHF experiments

The in vitro CHF experiments were performed using prepared porcine blood. Before the CHF experiments, the hemofilter (PS or NV-PS) and blood circuit (U-520, SZ-M; Junken Medical Co., Ltd., Tokyo, Japan) were primed with saline. Prepared porcine blood from one animal was divided into two portions (1 L each), and each potion was dispensed into a sterilized 1 L conical flask. The filtrate was not drained during the CHF experiment but was returned to the flask (permeate-recycle filtration). The flask was sealed to avoid air contamination, but a simple damper was also placed on the stopper of the flask to maintain the pressure in the flask and to ensure that the filtrate would be able to return to the flask quickly during the CHF experiment (Fig. 1).

After the saline was replaced with the blood, 300 mL of blood was allowed to flow into the circuit as a single-pass flow (100 mL of blood was discarded). The total blood volume inside the circuit, hemofilter, and conical flask was therefore 0.9 L (0.7 L in the flask and 0.2 L in the blood circuit and hemofilter).

During the CHF experiment, the blood in the conical flask was kept at 37 °C and was stirred using a rotator and a stirrer. The blood flow rate (Q_B) was set at 100 mL/min,

Fig. 1 Schematic diagram of the experimental circuit

and the flow rate of filtration (Q_F) was set at 20 mL/min; once the CHF experiment was started, the flow rate and pressure were monitored using a blood purification apparatus (TR-55X or TR-525; Toray Co., Ltd., Tokyo, Japan).

After the 24-h CHF experiment, the circulated blood was washed out using 0.5 L of saline at a flow rate of 100 mL/min without filtration, followed by 1.5 L of saline at a flow rate of 100 mL and a filtration rate of 20 mL/min. The residual blood clots were then evaluated.

Hematocrit, total protein concentration and ACT during CHF experiment

After the start of the CHF experiment, blood was collected from the sampling port on the arterial side of the blood circuit at 0 (just after start), 1, 3, 6, 20 and 24 h. The hematocrit level was measured using the microhematocrit method. The total protein concentration in the blood was measured using a refractometer (SUR-JE; Atago Co. Ltd., Tokyo, Japan). The ACT was measured using a microcoagulator. The continuous injection of heparin was adjusted to maintain the ACT of the circulating blood within a range of 300–400 s during the CHF circulation experiment. First, the heparin infusion rate was started at 50 units/h; it was then increased or decreased by 25 units/h if the ACT was 25 s shorter or longer than the previous measurement and increased by 50 units/h if the ACT was less than 315 s.

Evaluation of transmembrane pressures and pressure drop

The arterial side pressure (blood side inlet of the hemofilter: P_A), venous side pressure (P_V), filtrate side pressure (P_F), and transmembrane pressure (TMP) were recorded from the monitor of the blood purification machine (TR55X or TR525; Toray Medical Co., Ltd., Tokyo, Japan) every hour (or every 6 min after the start of a rapid increase in pressure). The TMP was calculated using Eq. (1):

$$\text{TMP} = (P_A + P_V)/2 - P_F \tag{1}$$

The pressure drop across the hemofilter was calculated by subtracting the venous side pressure from the arterial side pressure.

Amount of blood cells remaining in residual blood clots

The amount of blood cells in the residual blood clots was determined using a previously described method [18]. Briefly, 200 mL of saline solution containing 0.5% TritonX-100 (t-Octylphenoxypolyethoxyethanol; Fujifilm Wako Pure Chemical, Tokyo, Japan) was circulated through the hemofilter at a Q_B of 100 mL/min for 2 h to obtain an elute containing the hemoglobin and lactate dehydrogenase (LDH) in the blood cells that had adhered to the membrane. The lactate dehydrogenase (LDH)
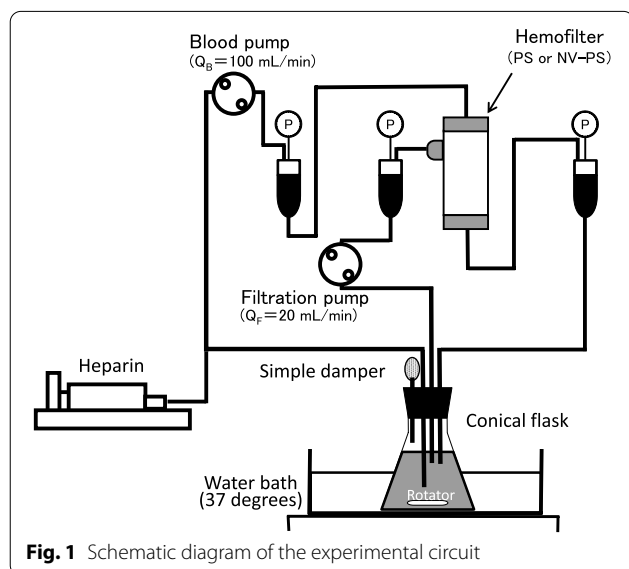
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activity in the eluate was then measured using an LDH detection kit (Cytotoxicity detection kit [LDH]; Roche Applied Science, Penzberg, Germany). The hemoglobin content in the eluate was also measured using a hemoglobin detection kit (Hemoglobin-B Test Wako; Fujifilm Wako Pure Chemical Corporation, Tokyo, Japan).

SC of dextran

Single-pass filtration experiments using dextran solution were performed at two timepoints: before and after 24 h of blood circulation. Five liters of dextran solution were prepared by adding 2.5 g of each dextran (molecular weights (MWs): 1500, 6000, 15,000–20,000, 40,000, 60,000 and 200,000; Sigma-Aldrich Japan KK, Tokyo, Japan) to a saline solution. The dextran solution was allowed to flow through the hemofilter for 20 min, and samples were collected at the inlet and outlet of the blood side and at the filtrate outlet. The dextran concentration of the sample was measured using gel permeation chromatography (HLC-8420GPC EcoSEC-Elite; Tosoh Co.) equipped with a refractive index detector and a TSK gel column (TSKgel-G3000PWXL, Tosoh Co.) at 40 °C and a flow rate of 1.0 mL/min. The SC was calculated using Eq. (2):

$$SC = 2C_F/(C_I + C_O) \tag{2}$$

where C_I is the inlet side concentration on the blood side, C_O is the outlet side concentration on the blood side, and C_F is the filtrate side concentration.

The MWs of dextran with SC of 0.1, 0.2, 0.3, 0.4 and 0.5 on the dextran MW cutoff curve were also calculated to compare solute removal performance of PS and NV-PS.

Statistics

Data are presented as the means ± standard deviation. A statistical analysis was performed using two-way ANOVA and post-hoc Tukey's test to compare the hematocrit (Ht), total protein concentration (TP), ACT, heparin infusion rate, TMP, and pressure drop between PS and NV-PS. A paired *t*-test was used to compare the change in the MW (SC) and coefficient of variation in the TMP and pressure drop for each SC between PS and NV-PS. The Wilcoxon signed-rank test was used to compare the hemoglobin content and the LDH activity between PS and NV-PS, because of an unequal variance in the data. A probability (*P*) value of < 0.05 was regarded as denoting statistical significance.

Results

Change in Ht, TP, ACT, and heparin infusion rate during CHF experiments

The Ht and TP did not change significantly during the 24-h CHF experiments (Fig. 2a,b), and the ACT

remained within the range of 300–400 s for both experiments (NV-PS and PS). No significant difference in ACT was observed (Fig. 2c). The initial continuous infusion rate for heparin was 50 units/h in both CHF experiments, and a similar time course was observed for both hemofilters (Fig. 2c). The ratio of the heparin infusion rate to the ACT, which was the amount of heparin required to maintain an ACT within a range of 300–400 s, increased after 6 h of circulation, compared with at the start of circulation, although the change was not significant; however, a significant reduction was observed after 24 h of circulation. No significant differences were observed between the PS and NV-PS (Fig. 2d).

TMP and pressure drop during CHF experiments

The TMP and pressure drop (pressure difference between arterial and venous drip chamber of blood circuit) were measured every hour during the CHF experiment. The TMP increased with time from the start of the CHF experiment until the end of the CHF experiment (Fig. 3a). The increase in the TMP for the NV-PS was significantly slower than that for the PS. The pressure drop across both filters increased with time from the start of the CHF experiment until the end of the experiment (Fig. 3b). The increase in the pressure drop was significantly slower for NV-PS than for PS. The coefficients of variation (standard deviation/mean) of the TMP and pressure drop were also compared. No significant difference was observed for the TMP (PS: 0.11 ± 0.01; NV-PS: 0.11 ± 0.01, $n = 25$), while the coefficient of variation of the pressure drop was significantly smaller for NV-PS than for PS (PS: 0.24 ± 0.05; NV-PS: 0.16 ± 0.02, $n = 25$, $p < 0.0001$).

Dextran SC of hemofilter membrane before and after CHF experiments

The SCs of the membranes for dextran were measured before and after the CHF experiment (Fig. 4). The cutoff curve of the NV-PS before the CHF experiment was located to the left of the curve for the PS, meaning that the pore size of the NV-PS was initially designed to be smaller than that of the PS membrane. The cutoff curves of both the NV-PS and PS had shifted to the left after 24 h of CHF, meaning that the pore size of both membranes had decreased after coming into contact with blood.

The MWs of dextran with SC of 0.1, 0.2, 0.3, 0.4 and 0.5 on the dextran MW cutoff curve were calculated (Fig. 5). The MWs after 24 h circulation were not significantly different between PS and NV-PS for SC = 0.1–0.5. When the SC was 0.1, 0.2, 0.3 or 0.4, the reductions in the MWs (SC = 0.1–0.4) with NV-PS were significantly lower than those with PS after circulation, implying that
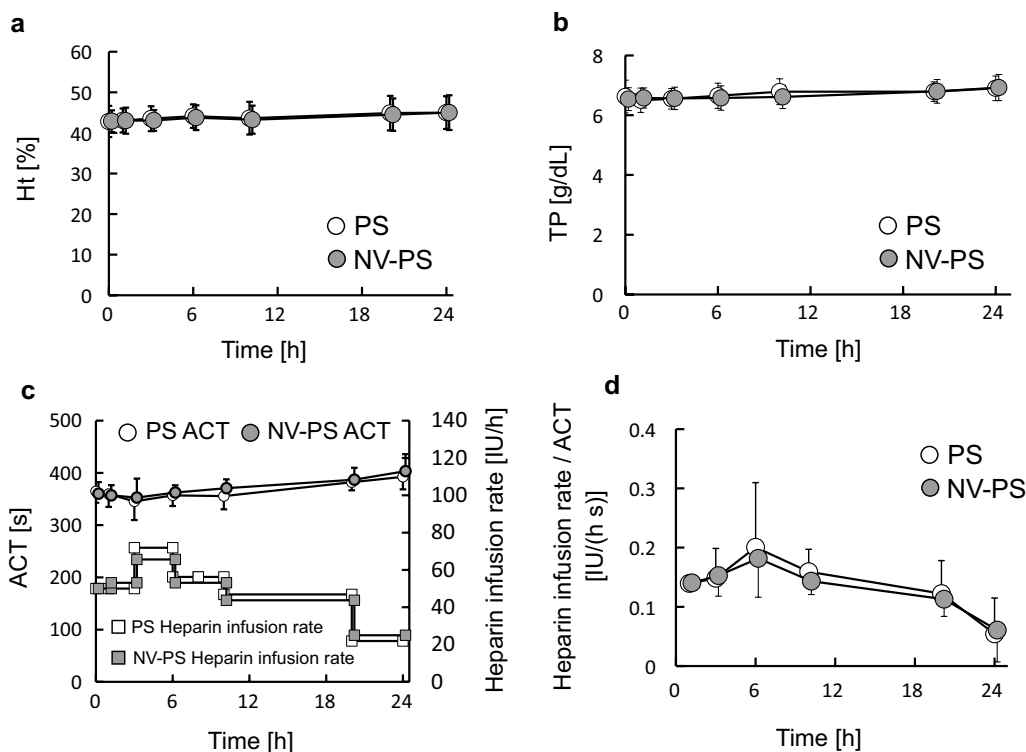
Fig. 2 Changes in **a** hematocrit (Ht), **b** total protein concentration (TP), **c** activated clotting time (ACT), and **d** heparin infusion rate of circulating blood during the CHF experiments. The Ht and TP levels remained unchanged throughout the CHF experiments. The ACT was maintained within a range of 300–400 s. The heparin infusion rate/ACT was significantly decreased for both membranes after 24 h of circulation. Data are expressed as the mean ± SD, $n = 8$
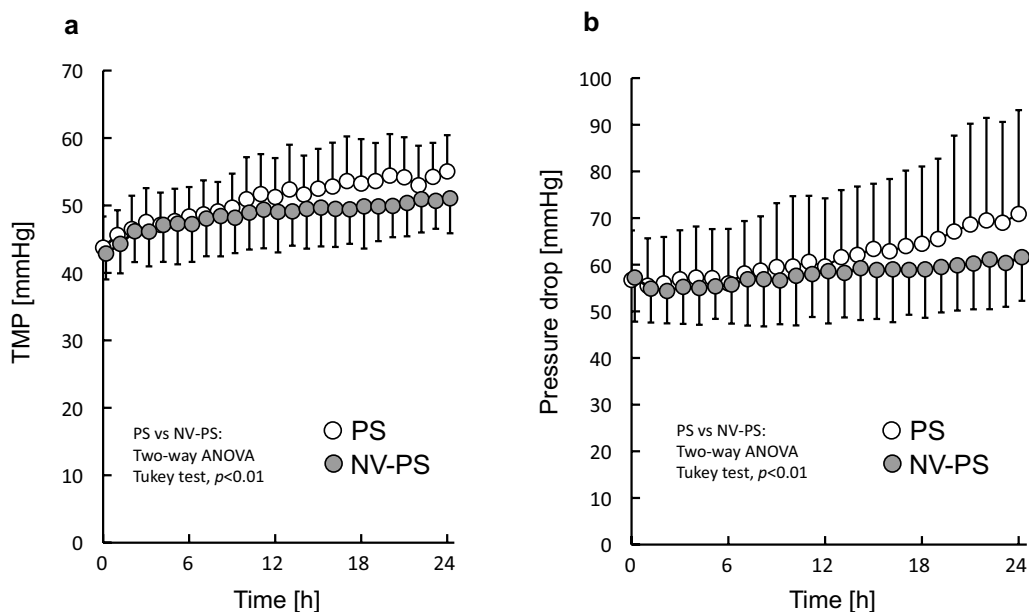

Fig. 3 Change in **a** TMP and **b** pressure drop across the hemofilters during the CHF experiments. The time courses of the TMP and pressure drop across the hemofilters during the 24-h CHF experiments showed slight increases with time. The increase in TMP and pressure drop for NV-PS were significantly slower than those for PS. Data are expressed as the mean ± SD, $n = 8$

NV-PS showed a lower degree of permeability reduction for larger molecules than PS.

Amount of blood cells remaining in residual blood clots

The amount of blood cells remaining in residual blood clots was evaluated by determining the hemoglobin content and the LDH activity of the eluate after 24 h of CHF (Fig. 6). The concentrations in the eluate after CHF using NV-PS were significantly lower than those after CHF using PS, indicating a higher degree of blood cell adherence to the PS membrane, including red blood cells captured within blood clots.

Discussion

The new findings of the present study were that NV-PS, a hydrophilic polymer (NV polymer)-embedded membrane, had the advantageous characteristics of (1) less fouling and less clogging of the hollow fibers during prolonged circulation, (2) a smaller reduction in sieving performance after blood contact, and (3) less adhesion of the blood cells and subsequent activation of the coagulation system, compared with a conventional membrane. These characteristics provide many advantages for using this membrane for continuous blood purification therapy in acute phase patients.

We evaluated the changes in solute permeability after blood contact and the antithrombotic properties of two types of hemofilters in a 24-h in vitro CHF experiment with a permeate recycle mode, which was developed as a modification of a single pass mode for in vitro CHF experiments [19]. In the single-pass mode, proteins and coagulation factors were removed faster during the 24-h experiment than during clinical settings because only 1 L of blood was used and the filtrate was discarded. In the present study, we used a permeate recycle mode, in which the filtrate flowed back into the blood tank, allowing us to perform the experiment while maintaining the concentrations of proteins and coagulation factors for a more extended period of time and increasing the likelihood of membrane fouling. We also changed the anticoagulant from the continuous administration of trisodium citrate and nafamostat mesylate to a single dose of trisodium citrate at the time of blood collection combined with a low dose of heparin. This created a more stringent experimental system for evaluating changes in filter performance and antithrombotic properties over 24 h, during which time the coagulation reaction was triggered
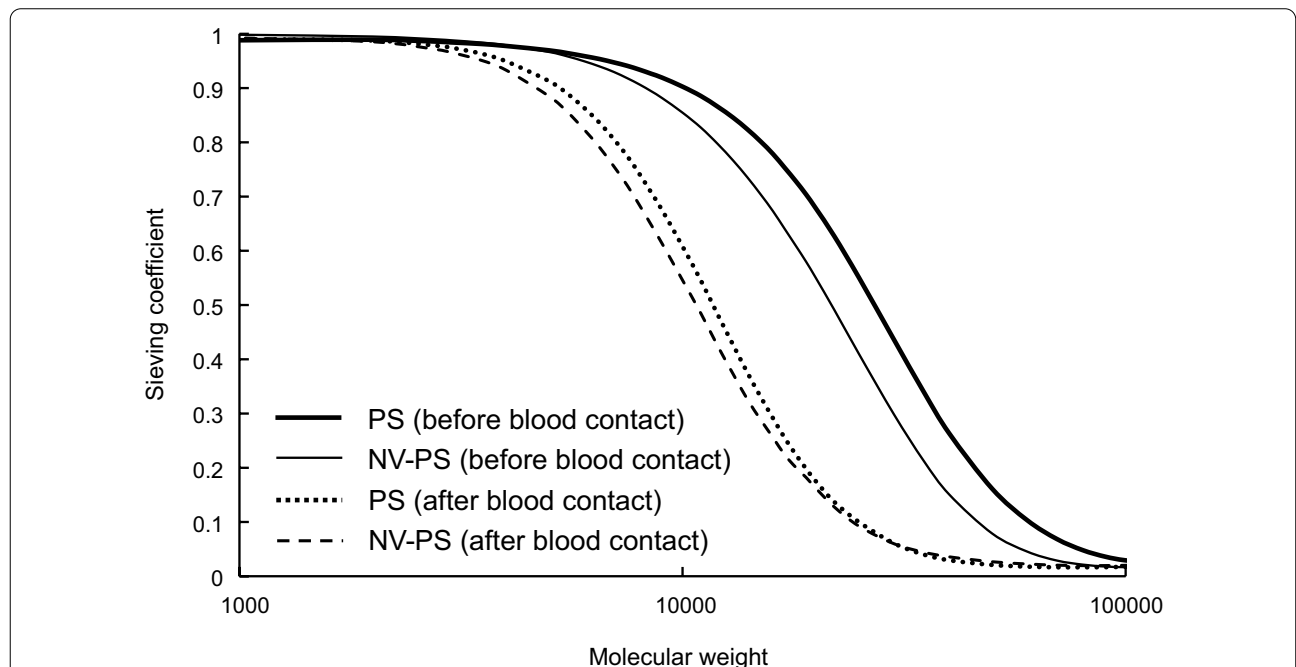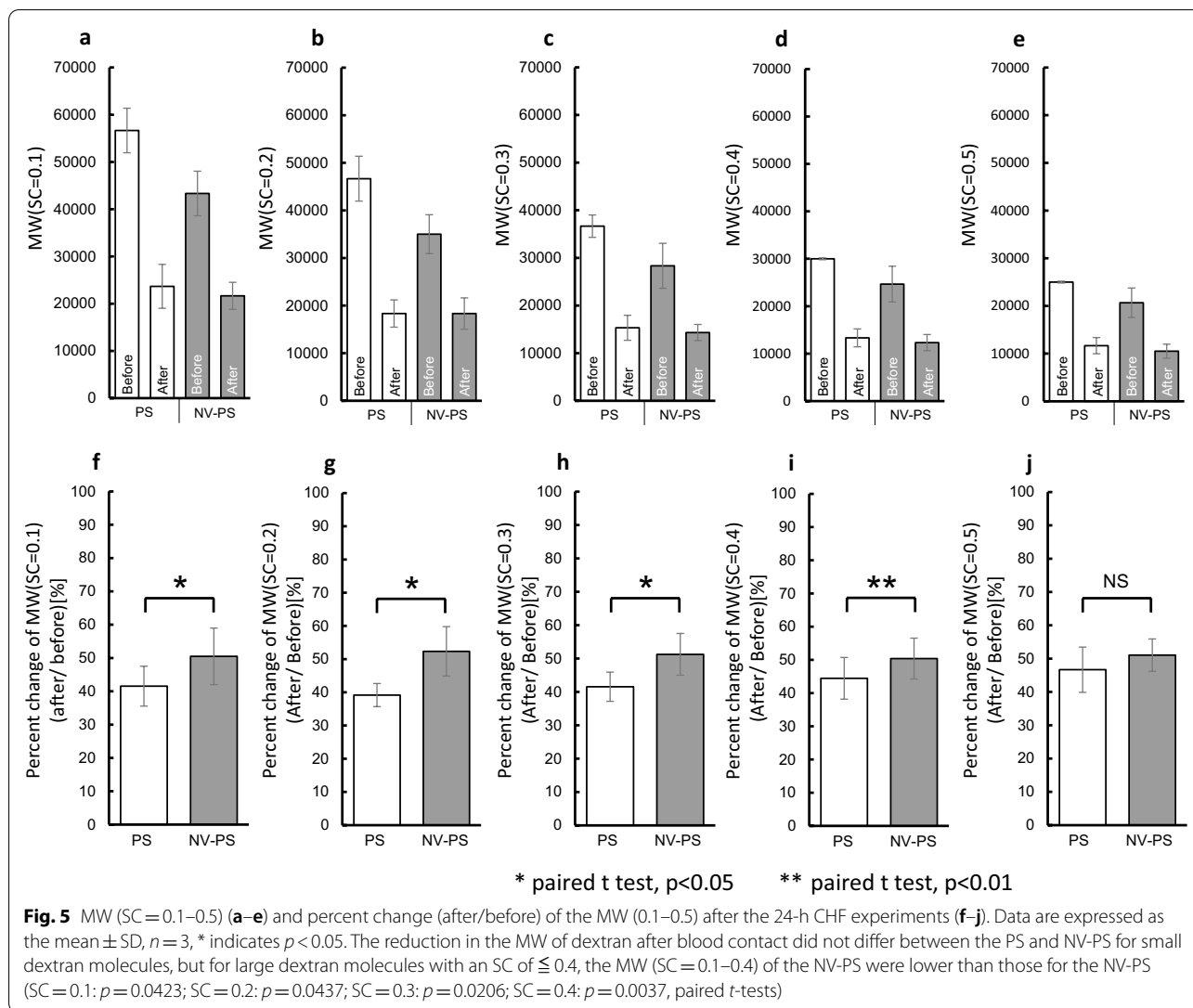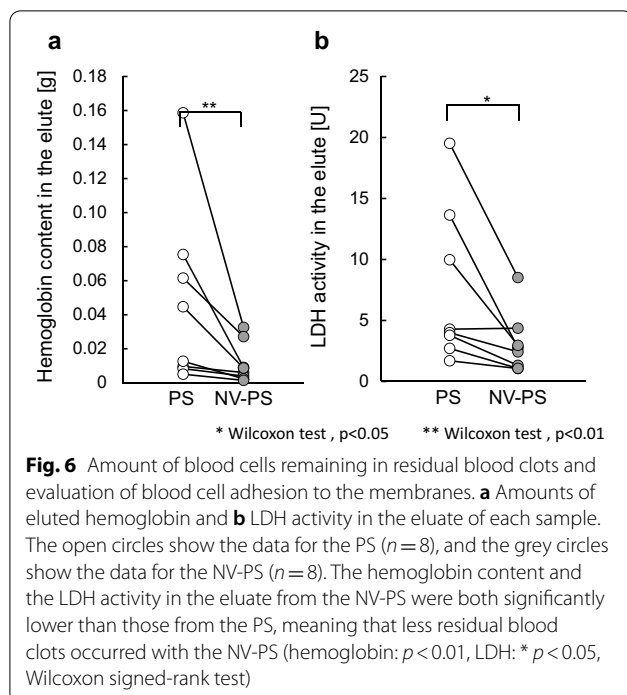

Fig. 4 MW cutoff curves of dextran molecules before and after the 24-h CHF experiments. The cutoff curve for the NV-PS hemofilter before the CHF experiment was located to the left of the curve for the PS hemofilter. The cutoff curves of both the NV-PS and PS hemofilters had shifted to the left after 24 h of CHF. Data are expressed as the mean (*n* = 3)

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Fig. 5 MW (SC = 0.1–0.5) (**a**–**e**) and percent change (after/before) of the MW (0.1–0.5) after the 24-h CHF experiments (**f**–**j**). Data are expressed as the mean ± SD, $n = 3$, * indicates $p < 0.05$. The reduction in the MW of dextran after blood contact did not differ between the PS and NV-PS for small dextran molecules, but for large dextran molecules with an SC of ≦ 0.4, the MW (SC = 0.1–0.4) of the NV-PS were lower than those for the NV-PS (SC = 0.1: $p = 0.0423$; SC = 0.2: $p = 0.0437$; SC = 0.3: $p = 0.0206$; SC = 0.4: $p = 0.0037$, paired *t*-tests)

by factor XII in the intrinsic blood coagulation pathway. The ACT was periodically adjusted to within the range of 300–400 s, enabling a more stable experimental system than the previous experimental model and making it easier to evaluate membrane-blood interactions under conditions where membrane fouling and coagulation were more likely to occur. A limitation of this experimental model is that the experiment should be completed within 24 h to obtain reliable results. Because the ratio of heparin infusion rate to ACT was significantly reduced for both membranes at 24 h, the coagulation capacity had most likely been reduced at this time point.

The TMP and pressure drop across both hemofilters showed a slight increase during the CHF experiments. Both the TMP and pressure drop across the hemofilter were lower for the NV-PS than for the PS (Fig. 3a). An increase in the TMP indicates membrane fouling occurring as a result of narrowing or blockage of the membrane pores. Since the SC was mainly affected by the pore size of the membrane, the change in the MW cutoff curves for dextran showed that the NV-PS originally had a smaller pore size and that the decrease in pore size after the CHF experiment was also smaller, as compared with the observations for the PS. In a study comparing the SCs of PS after 1 h and 24 h of circulation, the values were found to remain almost unchanged [18], suggesting that there was little change in the SC (pore size) during this period. Narrowing of the pore size is considered to occur in the early phase after blood contact and to remain almost unchanged for 24 h. On the other hand, hydraulic permeability, which affects the TMP, not only varies with the pore size, but also with the porosity (number of pores) and pore length (thickness of the skin and support layers). While the initial TMP of PS and NV-PS were

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Fig. 6 Amount of blood cells remaining in residual blood clots and evaluation of blood cell adhesion to the membranes. **a** Amounts of eluted hemoglobin and **b** LDH activity in the eluate of each sample. The open circles show the data for the PS ($n=8$), and the grey circles show the data for the NV-PS ($n=8$). The hemoglobin content and the LDH activity in the eluate from the NV-PS were both significantly lower than those from the PS, meaning that less residual blood clots occurred with the NV-PS (hemoglobin: $p<0.01$, LDH: * $p<0.05$, Wilcoxon signed-rank test)

almost the same, they gradually increased for PS. Since there was no change in the SC during this period[18), we consider that the increase in TMP (decrease in hydraulic permeability) was mainly caused by pore blockage, which gradually increased during the 24 h. The reduction in the MW of dextran for the same SC after blood contact did not differ between PS and NV-PS for small dextran molecules, but for large dextran molecules with an SC of $\leqq 0.4$, the MW (SC = 0.1–0.4) of NV-PS was lower than that of PS. These results indicate less fouling, i.e., a smaller performance reduction of the membrane for NV-PS.

The pressure drops during the CHF experiments were significantly smaller for NV-PS than for PS (Fig. 3b), suggesting a greater degree of clogging of the hollow fibers of PS than of NV-PS. The amount of residual blood cells, as evaluated by the hemoglobin content and LDH activity of the eluate, was smaller in NV-PS than in PS. Both of these results suggest a lower degree of clogging of the hollow fibers in NV-PS as compared with PS. PS also showed a greater degree of variation of the pressure drop for residual blood clots as compared with NV-PS. The blood used in this study was considered to include both blood that was likely to coagulate and not likely to coagulate. The PS membrane was particularly prone to clogging of the hollow fibers when the blood was likely to coagulate, resulting in a larger variation of the pressure drop and more hollow fiber clogging. Therefore, NV-PS might be a more stable filter that is not easily prone to clogging of the hollow fibers, even with blood that is likely

to coagulate. The hemoglobin contents and LDH activity also showed larger variations in PS than in NV-PS membrane. This result showed that when the blood was likely to coagulate, more residual blood clots was observed in PS, but less residual blood clots in NV-PS, whereas when the blood was not likely to coagulate, little difference in the amount of residual blood clots was observed between PS and NV-PS. Even when there was a small difference in the amount of residual blood clots, the amount of residual blood clots in NV-PS was still smaller than that in PS. We have not excluded the results showing large differences, because we were able to continue the CHF experiment for 24 h included in the analysis. We considered that the coagulation properties of all the blood used in these experiments were within the range of variations in the blood of patients in actual clinical practice. Since the PS was developed as a filter with a low residual blood clots property [18], we created a more stringent experimental model that allowed us to compare the antithrombotic properties in greater detail when evaluating the basic performances of such membranes. Reportedly, NV polymer adsorbs less fibrinogen [13], which prevents platelet adhesion [15] and reduces direct platelet and neutrophil activation [14]. Use of NV-PS for 24-h CHF treatment in clinical situations could also be expected to enable a reduction in blood cell adhesion and less clogging of the hollow fibers for the same reasons. Since the adhesion of platelets and other blood cells to the membrane was lower, the subsequent coagulation reactions could be inhibited during CHF, and inhibition of biologically incompatible reactions could also be expected.

In conclusion, we modified a 24-h in vitro CHF experimental model to create a more stringent CHF experimental model with a permeate-recycle mode to compare NV-PS and PS. This model enabled us to examine the reduction in the solute removal performance and anticoagulant properties of the two membranes under stringent conditions. The solute removal performance after blood contact of NV-PS was the same as that of PS, even though the original pore size of NV-PS was smaller than that of PS. NV-PS has the advantages of showing less adhesion of blood cells and subsequent blood coagulation, a lower degree of reduction of the solute removal performance, and less clogging of the hollow fibers during prolonged circulation. In particular, in terms of the pressure drop and residual blood clots, NV-PS can be expected to show less variations depending on the blood coagulation properties, and to exhibit a solute removal performance close to that originally designed. These characteristics may be expected to prove advantageous when this membrane is used for continuous blood purification therapy in acute-phase patients.

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Author contributions

KoKo and YK designed the research, performed the experiment and data analysis, and wrote the manuscript; SU performed the experiment and data analysis; KeKo, MK and HK provided the working hypothesis, participated in the research design, and substantially contributed to the study concept. All the authors read and approved the final manuscript.

Availability of data and materials

The datasets analyzed during this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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