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RESEARCH

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# Effect of hollow fiber diameter and membrane surface area of polymethyl methacrylate membrane on filter lifetime

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## Abstract

**Background** When polymethyl methacrylate (PMMA) membranes are used in continuous renal replacement therapy, especially in patients with high cytokine levels, inflammatory cytokines and other substances are removed by the adsorption effect. However, such filters are prone to clogging, and the filter lifetime can be short. This study investigated the effects of hollow fiber inner diameter and membrane area on filter lifetime and protein removal performance using an in vitro continuous hemofiltration (CHF) experimental model with porcine blood.

**Methods** Three types of filters with different hollow fiber inner diameters and membrane areas were used: CH-1.0N (membrane material, PMMA; membrane area, 1.0 $m^2$; hollow fiber inner diameter, 200 μm), CH-1.0W (prototype: PMMA; 1.0 $m^2$; 240 μm), and CH-1.8W (PMMA; 1.8 $m^2$; 240 μm). During the experiment, pressure changes, filter lifetime measured from pressure and protein removal performance were measured using an in vitro CHF experimental model with porcine blood.

**Results** The filter lifetime of CH-1.8W was significantly longer than those of CH-1.0N and CH-1.0W. The total protein adsorption was significantly higher for the CH-1.0W and CH-1.8W filters than for the CH-1.0N filter.

**Conclusions** A larger membrane area from 1.0 to 1.8 $m^2$ contributed to a longer filter lifetime, while an increase in the hollow fiber inner diameter from 200 to 240 μm did not. On the other hand, the protein removal performance, especially the adsorption performance, was higher for membranes with a larger hollow fiber inner diameter from 200 to 240 μm.

**Keywords** Filter lifetime, Membrane area, Hollow fiber inner diameter, Polymethyl methacrylate membrane

## Introduction

Since polymethyl methacrylate (PMMA) membranes can remove inflammatory cytokines by adsorption, they are thought to have therapeutic effects in continuous renal replacement therapy (CRRT), especially for conditions with high cytokine concentrations [1, 2]. Inflammatory cytokine levels decreased after passage through a PMMA membrane, compared with before passage through the PMMA membrane [3], and the use of a PMMA membrane resulted in a persistent decrease in inflammatory cytokine levels three days after treatment, compared with

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before treatment [4]. As well, the use of a PMMA membrane with a high adsorption effect improved the survival rate of patients with sepsis and undergoing CRRT, compared with the use of a non-adsorbed membrane [5]. Polymyxin B immobilized fiber column direct hemoperfusion followed by PMMA-CHDF (continuous hemodiafiltration) significantly reduced the sequential organ failure assessment score three days after treatment, compared with the pre-treatment score [6], and increasing the membrane area resulted in a faster decrease in blood cytokine levels [7] and a significantly higher intensive care unit survival rate [8]. In addition, the adsorption of various proteins on PMMA membranes after treatment has been confirmed [9].

However, the lifetime of PMMA membranes has been reported to be relatively short [10], although another recent report concluded that the lifetime of PMMA membrane filters was similar to those of other membranes [11]. Thus, a consensus on the lifetime of PMMA membranes does not exist. In clinical evaluations, comparing filters under the same constant conditions is difficult because of differences in the patients' conditions at the start of treatment and changes in their conditions during treatment. The development of membranes and filters requires that the lifetimes of membranes be evaluated under stable conditions as a basic performance criterion. Therefore, we established an in vitro experimental model using porcine blood [12]. This model was established by changing the concentration of trisodium citrate added to the substitution fluid as an anticoagulant. The model was able to evaluate membrane clogging occurring as a result of fouling under the same conditions.

Frequent clotting occurring during CRRT results in inadequate solute removal, an increased cost for the circuit and filter, time loss for the staff, and an increased risk of problems [13]. If the lifetimes of PMMA membrane filters with high cytokine adsorption could be extended, the burden on staff would be reduced and the benefit to the patient would be increased. For this reason, a PMMA membrane filter (CH-1.8W) with a membrane area of 1.8 $m^2$ and a hollow fiber inner diameter of 240 μm has been developed and used for CRRT. In a report comparing the lifetime of the CH-1.8W filter and filters without adsorption properties in clinical practice, the 24-h achievement rate of the CH-1.8W filter was reported to be the same as that of 2.1 $m^2$ CTA membranes [14], while the lifetime of the CH-1.8W filter was significantly longer than that of 1.0 $m^2$ PS membranes [15]. Both the membrane area and the hollow fiber inner diameter of the CH-1.8W filter are larger than those of the conventional CH-1.0N filter. How these factors affect filter lifetime and protein removal performance are uncertain. The aims of the present study were to clarify how the lifetime and protein removal characteristics of filters change as the hollow fiber inner diameter and membrane area are increased using an in vitro evaluation model that enables filters to be evaluated under the same conditions.

## Methods

### Preparation and procedure for continuous hemofiltration (CHF) experiments

CH-1.0N (membrane material: PMMA, membrane area: 1.0 $m^2$, hollow fiber inner diameter: 200 μm; Toray Industries, Inc., Tokyo, Japan), CH-1.0W (prototype, membrane material: PMMA, membrane area: 1.0 $m^2$, hollow fiber inner diameter: 240 μm, prototype; Toray Industries, Inc., Tokyo, Japan), and CH-1.8W (membrane material: PMMA, membrane area: 1.8 $m^2$, hollow fiber inner diameter: 240 μm; Toray Industries, Inc., Tokyo, Japan) were used in a long-term in vitro experiment using porcine blood to simulate CHF (Table 1).

The experimental method was previously reported [12]. Briefly, porcine blood was collected from a single animal and divided into three portions of 1 L each (0.7 L in a soft bag and 0.3 L for the blood circuit and hemofilter); each portion was used for one CHF experiment. All experiments were conducted under the same conditions: the blood flow rate ($Q_B$) was 100 mL/min, and the flow rate of the replacement fluid ($Q_S$) and filtrate ($Q_F$) was 10 mL/min.

Blood preparation was performed in the same manner as previously reported [12]. The hematocrit level (HCT) and the total protein concentration (TP) in the porcine blood used in this study were 40.4 ± 4.4% and 6.6 ± 0.3 g/dL, respectively.

Anticoagulants used were nafamostat mesylate and trisodium citrate. Nafamostat mesylate (Coahibitor®; AY Pharmaceuticals Co., Ltd. Tokyo, Japan) was injected into the blood circuit from the blood side inlet; a 20 mg bolus injection was used at the start of the CHF experiment, and a 20 mg/h continuous injection was used during the experiment. The concentration of trisodium citrate

**Table 1** Technical data on hemofilter used

| | CH-1.0N | CH-1.0W | CH-1.8W |
|---|---|---|---|
| Membrane material | Polymethyl methacrylate | | |
| Membrane surface area [$m^2$] | 1.0 | | 1.8 |
| Hollow fiber diameter [μm] | 200 | 240 | |
| Hollow fiber thickness [μm] | 30 | | |
| Effective length [cm] | 19.5 | | |
| Number of hollow fibers (calculation) [–] | 8161 | 6801 | 12,243 |
| Hydraulic permeability [mL/mmHg/$m^2$/h] | 33.0 ± 2.3 | 32.4 ± 4.6 | 32.5 ± 4.6 |

(Wako Pure Chemical Industries, Ltd., Osaka, Japan) in the circulating blood was maintained at 7 mM (final concentration) during the CHF through the addition of substitution fluid trisodium citrate (7 mM).

The experiment was continued until the arterial side pressure ($P_A$) or transmembrane pressure (TMP) reached 400 mmHg or until 48 h had elapsed from the start of the experiment.

Water permeability was measured before the experiment. The pressure change, total protein concentration in the blood, and total protein permeability in the filtrate were measured over time during the CHF experiment.

### Measurement and calculations of pressures

The $P_A$, venous side pressure ($P_V$), filtrate side pressure ($P_F$), and 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 and pressure drop across the hemofilter ($\Delta P_B$) were calculated using Eqs. (1) and (2):

$$\mathrm{TMP} = \frac{P_A - P_V}{2} - P_F \tag{1}$$

$$\Delta P_B = P_A - P_V \tag{2}$$

From the results of the pressure changes, the time at which the TMP increased by more than 15 mmHg/h (corresponding to the time at which the membrane pores started to clog), the time at which the TMP reached 200 mmHg (corresponding to the time at which the membrane pores began to clog), the time at which the $\Delta P_B$ increased by more than 15 mmHg/h (corresponding to the time at which the hollow fibers began to clog), and the time at which the $\Delta P_B$ reached 200 mmHg (corresponding to the time at which the hollow fibers began to clog) were calculated. The value of 200 mmHg was selected as the appropriate threshold, as it represents 2/5ths of the limit of the membrane pressure resistance (500 mmHg). The value of 15 mmHg/h was selected, as the variation in this value arising from measurement error during stable periods was within 15 mmHg/h (the maximum value was 13.5 mmHg/h) [12]. The TMP and $\Delta P_B$ values were also compared when the pressure was stable (0–3 h) for all conditions.

### Protein removal properties

Samples were collected from the arterial side of the blood circuit at 0, 1, 3, 6, 10, 20, 30, and 48 h. The total protein concentration in the blood was measured using a refractometer (SUR-JE; Atago Co. Ltd., Tokyo, Japan). The total protein concentration in the filtrate was measured using the pyrogallol red method (Micro TP Test Wako; FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan). The total blood protein removal was calculated by multiplying the total protein concentration in the blood by the plasma volume. The total filtrate protein permeation was calculated by multiplying the total protein permeability in the filtrate by the filtrate volume. The difference between the total blood protein removal volume and the filtrate total protein permeation volume was evaluated as the total protein adsorbed on the PMMA membrane.

### Statistics

In this study, the Friedman test was used to examine the filter lifetime. A two-way ANOVA with a post-hoc Bonferroni test was used to examine TMP and the pressure drop, the total protein concentration in the blood, the total protein permeability in the filtrate, and the total protein adsorbed on the PMMA membrane.

## Results

Each pressure during the experiment for each of the three filters was recorded at one-hour intervals. TMP and $\Delta P_B$ were calculated from the results (Fig. 1A, C). The dTMP/dt and $d\Delta P_B/dt$ values were calculated from TMP and $\Delta P_B$, respectively (Fig. 1B, D). No change in pressure was seen from just after the start of the experiment until some time had passed. The TMP, $\Delta P_B$, dTMP/dt, and $d\Delta P_B/dt$ each increased after a certain time in almost all the experiments.

The TMP and $\Delta P_B$ are shown for when the pressure was stable (0–3 h) in all the experiments. The TMP was significantly lower for the CH-1.8W filter, which had a larger membrane area, than for the CH-1.0N and CH-1.0W filters, which had smaller membrane areas ($p < 0.01$). The $\Delta P_B$ of the CH-1.8W filter with the larger membrane area was significantly lower than those of the CH-1.0W and CH-1.0N filters with smaller membrane areas ($p < 0.01$). When the two filters with the same membrane area were compared, the $\Delta P_B$ of the CH-1.0W filter, which had a larger hollow fiber inner diameter, was significantly lower than that of the CH-1.0N filter, which had a smaller inner diameter ($p < 0.01$) (Fig. 2).

The time when the TMP reached 200 mmHg, which was evaluated as the time when the pores of the membrane became clogged, and the time when the dTMP/dt increased by more than 15 mmHg/h, which was evaluated as the time when the pores of the membrane began to clog, were compared among the three types of membranes (Fig. 3A, B). The time at which the TMP reached 200 mmHg was significantly longer for the CH-1.8W filter than for the CH-1.0N and CH-1.0W filters ($p < 0.05$). The time when the dTMP/dt increased by more than 15 mmHg/h was also significantly longer for the

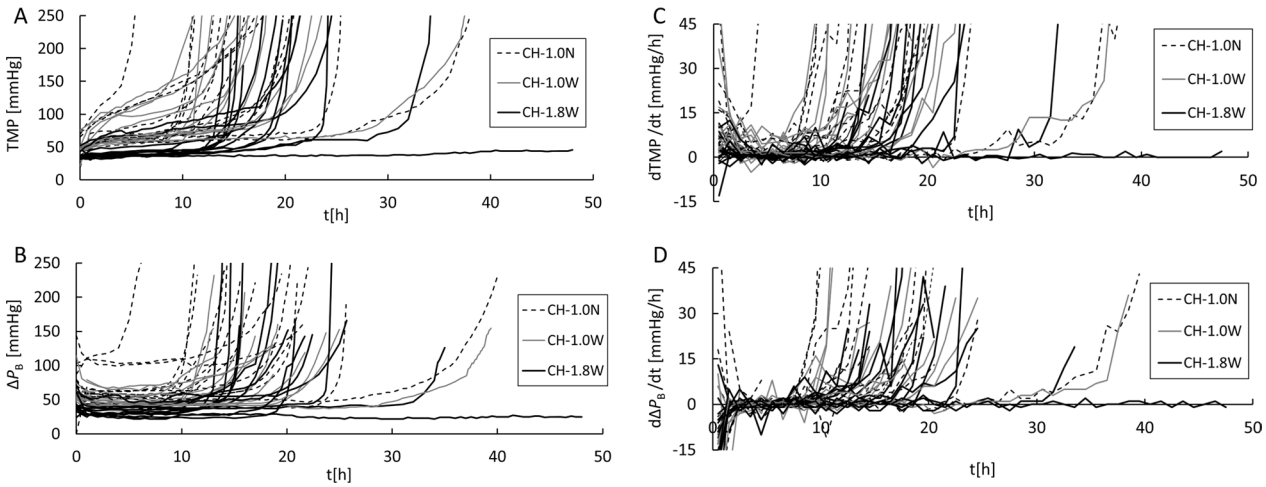


**Fig. 1** Time-course of TMP **A** pressure drop ($\Delta P_B$) across the hemofilter **B**, a derivative of TMP, dTMP/dt **C** and the derivative of the pressure drop, $d\Delta P_B/dt$ **D** for each filter. dP/dt was calculated from the TMP or pressure drop measured every hour (or every 6 min during steep increases). The TMP, the TMP derivative, the $\Delta P_B$, and the $\Delta P_B$ derivative remained stable and constant over several hours and then rapidly increased after a constant period

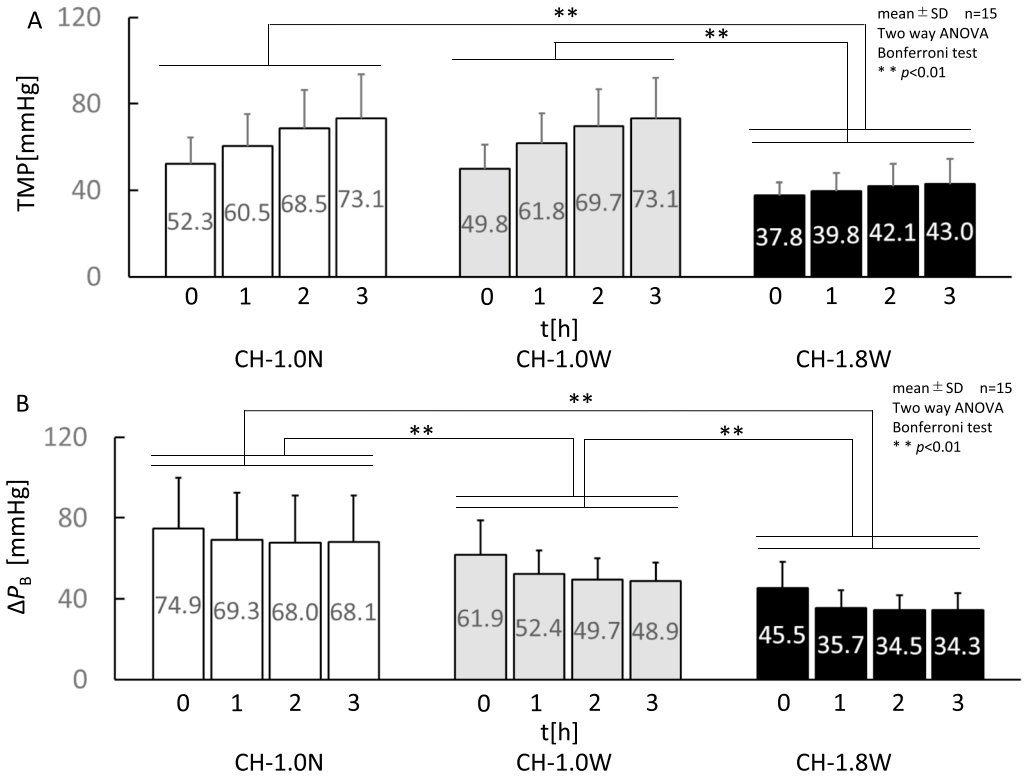


**Fig. 2** TMP **A** and pressure drop **B** when the pressure was stable in all the experiments. The TMP was significantly lower for the CH-1.8W filter than for the CH-1.0W and CH-1.0N filters. The pressure drop was significantly lower for the CH-1.8W filter than for the CH-1.0W and CH-1.0N filters, and that for the CH-1.0W filter was lower than that for the CH-1.0N filter

CH-1.8W filter than for the CH-1.0N and CH-1.0W filters ($p < 0.05$ for CH-1.0W vs. CH-1.8W, $p < 0.01$ for CH-1.0N vs. CH-1.8W). The time at which the $\Delta P_B$ reached 200 mmHg, which was evaluated as the time at which the hollow fibers themselves became clogged, and the time at which the $d\Delta P_B/dt$ increased by more than 15 mmHg/h,

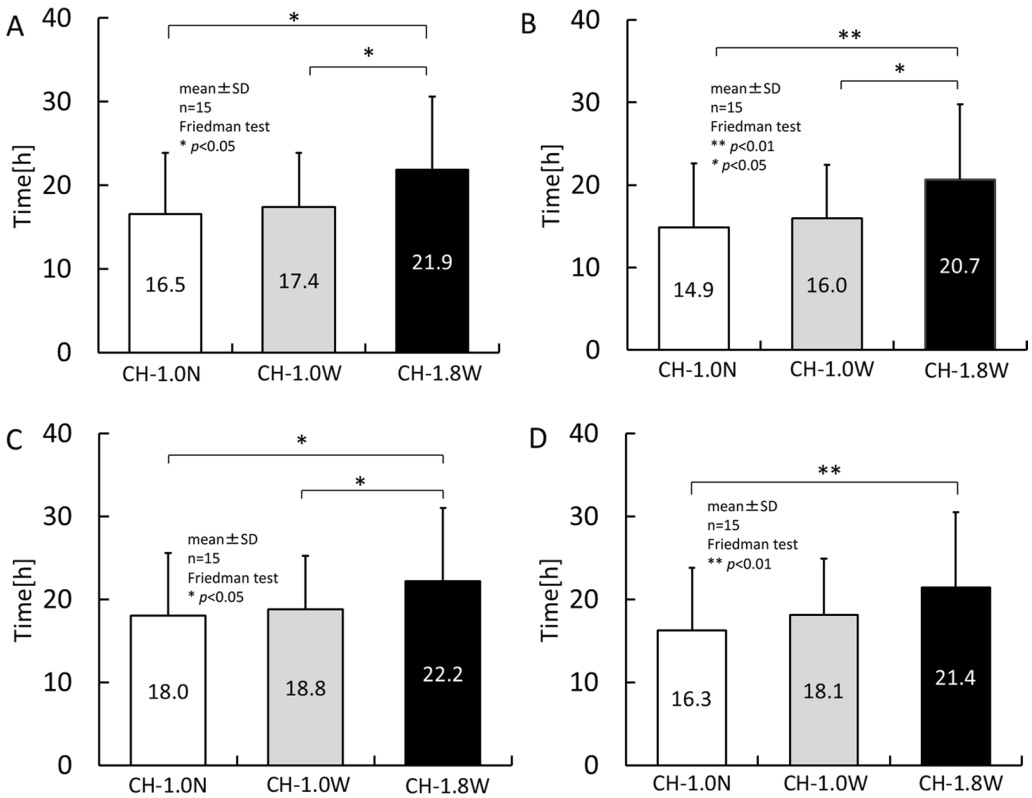


**Fig. 3** Times at which the TMP reached 200 mmHg **A**, the dP/dt of the TMP reached 15 mmHg/h **B**, the pressure drop across the hemofilter reached 200 mmHg **C**, and the dP/dt of the pressure drop reached 15 mmHg/h **D**. The times at which the TMP reached 200 mmHg, the dP/dt of the TMP reached 15 mmHg/h, and the pressure drop reached 200 mmHg were significantly longer for the CH-1.8W filter than for the CH-1.0N and CH-1.0W filters. The time at which the dP/dt of the pressure drop reached 15 mmHg/h was significantly longer for the CH-1.8W filter than for the CH-1.0N filter

which was evaluated as the time at which the hollow fibers themselves began to clog, were compared among the three types of membranes (Fig. 3C, D). The time at which the $\Delta P_B$ reached 200 mmHg was significantly longer for the CH-1.8W filter than for the CH-1.0N and CH-1.0W filters ($p < 0.05$). The time when the $d\Delta P_B/dt$ increased by more than 15 mmHg/h was significantly higher for the CH-1.8W filter than for the CH-1.0N filter ($p < 0.01$).

Regarding the total protein concentration in the blood and in the filtrate protein and the total protein adsorption on the PMMA membrane, the results at up to 6 h after the start of the experiment, when all the data points were available, were compared among the three types of membranes (Fig. 4). The total protein concentration in the blood decreased with time. The total protein concentration in the blood was significantly lower in the experiments using the CH1.0W and CH-1.8W filters than in the experiment using the CH-1.0N filter ($p < 0.05$ for CH-1.0N vs. CH-1.0W, $p < 0.01$ for CH-1.0N vs. CH-1.8W). No significant difference in the total protein permeability of the filtrate was observed among the three types of filters. The total protein adsorbed on the PMMA membrane was significantly higher for the CH1.0W and CH-1.8W filters than for the CH-1.0N filter ($p < 0.01$).

## Discussion

The main findings of the present study were as follows: (1) the filter lifetime was significantly prolonged by increasing the membrane area; (2) the total protein concentration in blood decreased with time and was significantly lower for filters with a larger membrane area and a larger hollow fiber inner diameter.

No significant difference in water permeability was seen among the three types of hemofilters prior to the start of the experiments. Therefore, the effect of differences in water permeability does not need to be taken into account in this study, and the membrane area and hollow fiber inner diameter were thought to have direct influences on the results. When the membrane permeability was the same and the same filtration flow rate was used, the larger membrane area had a lower filtration flow rate per unit of membrane area; theoretically, this would result in a lower TMP. Therefore, the CH-1.8W filter had a significantly lower TMP than the CH-1.0N

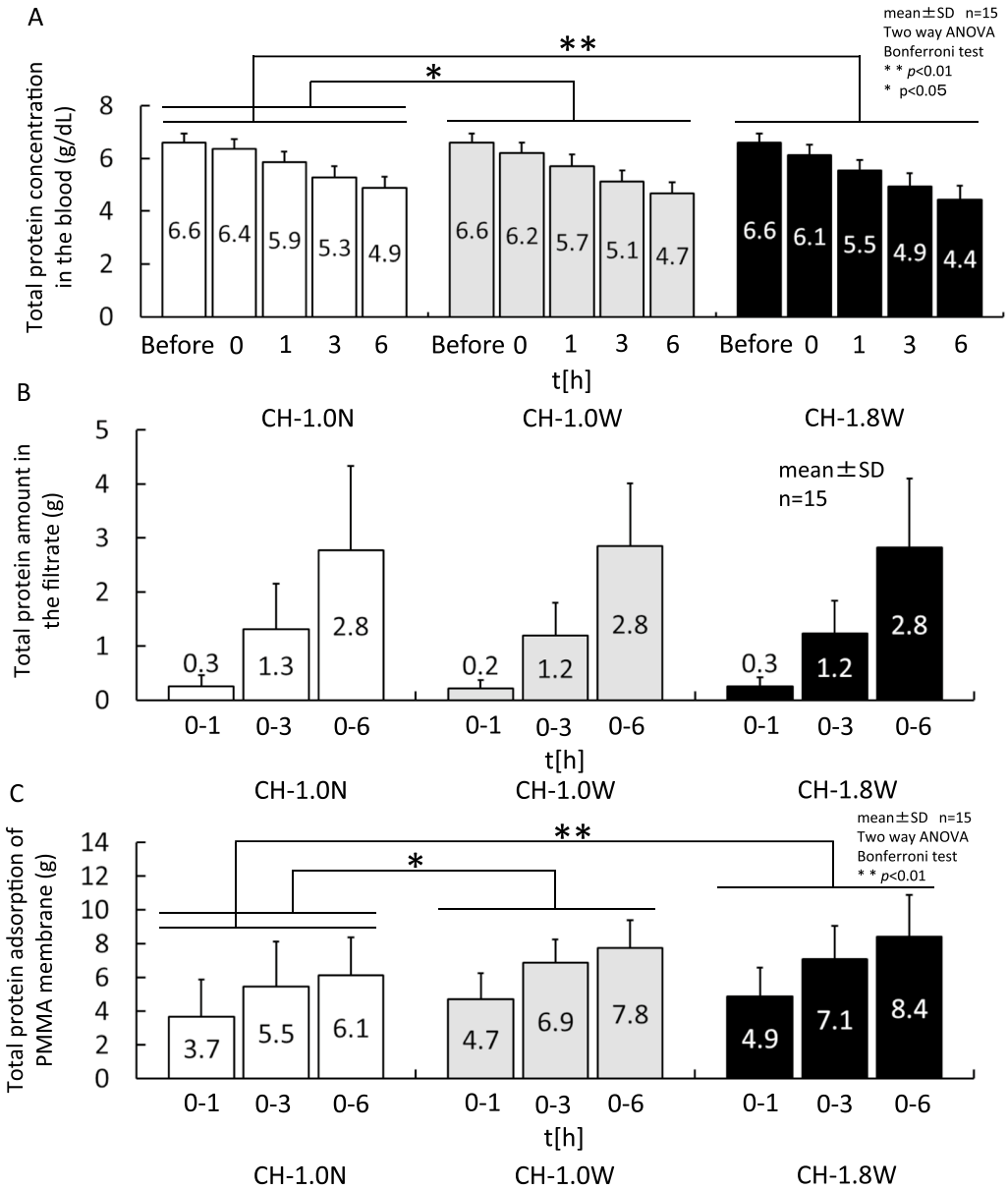


**Fig. 4** Total protein concentration in the blood **A** total protein concentration in the filtrate **B** and total protein adsorption on the PMMA membrane **C** The total protein concentration in the blood had significantly lower for the CH-1.0W and CH-1.8W filters than that for the CH-1.0N filter. The total protein adsorption of the PMMA membrane had significantly higher for the CH-1.0W and CH-1.8W filters than that for CH-1.0N filter

and CH-1.0W filters when the pressure was stable. The low TMP also indicates that the flow (filtration flux) to the membrane surface was low, which is thought to reduce the occurrence of clogging. Therefore, the time at which the pores of the hollow fibers began to clog and the time at which the pores of the hollow fibers became clogged were significantly longer for the CH-1.8W filter with a larger membrane area, compared with the other filters with smaller membrane areas.

The lifetime of the filter was significantly prolonged by increasing the membrane area. Converting the Hagen-Poiseuille equation, the $\Delta P_B$ is inversely proportional to the number of hollow fibers and the fourth power of the hollow fiber radius. Therefore, the more hollow fibers and the larger the inner diameter of the hollow fibers, the smaller the $\Delta P_B$ becomes. The $\Delta P_B$ of the CH-1.8W filter, which had a larger membrane area (same effective length but larger number of hollow fibers [Table 1]), was

significantly lower than those of the CH-1.0W and CH-1.0N filters, which had fewer hollow fibers. In addition, the CH-1.0W filter with a larger hollow fiber inner diameter had a significantly lower $\Delta P_B$ than the CH-1.0N filter with a smaller inner diameter, even though the membrane area was the same. However, the time at which the hollow fibers themselves began to clog was longer for the CH-1.8W filter than that for the CH-1.0N filter, and the time when the hollow fibers themselves became clogged was significantly longer for the CH-1.8W filter than for the CH-1.0N and CH-1.0W filters. However, no significant difference was seen between the CH-1.0N and CH-1.0W filters. This suggests that the membrane area, and not the hollow fiber inner diameter, primarily influences the filter lifetime.

The total protein concentration in the blood was significantly lower for the CH-1.8W and CH-1.0W filters than for the CH-1.0N filter. The sieving coefficient increases with decreasing blood flow velocity in hollow fibers and decreases with a decreasing local filtration flux [16]. In the present study, the blood flow velocity was CH-1.0N > CH-1.0W > CH-1.8W, and the local filtration flux was CH-1.0N = CH-1.0W > CH-1.8W. As the local filtration flux of CH-1.0N and CH-1.0W with different hollow fiber inner diameters was the same, the sieving coefficient would be expected to be affected only by the blood flow velocity. Therefore, the sieving coefficient of CH-1.0W, with the lower blood flow velocity, would be higher. As the sieving coefficient is higher, more proteins will pass through the pores, and the amount of total protein removed from the blood and amount of protein adsorbed in the membrane will also increase. In fact, the experimental results showed that the blood protein concentration was smaller when CH-1.0W rather than CH-1.0N was used, meaning that the total protein removal from the blood and the total protein adsorption in the membrane were greater for CH-1.0W than for CH-1.0N. On the other hand, in the comparison of CH-1.0W and CH-1.8W, both the blood flow velocity and local filtration flux were smaller for CH-1.8W. The blood flow velocity and local filtration flux exert opposite effects on the sieving coefficient, so that blood protein concentration decrease was nearly the same for CH-1.0W and CH-1.8W. The decrease in total protein concentration in the blood and increase in the total protein adsorbed in the PMMA membrane were the highest for the CH-1.8W (not significant), but whether this would serve as an advantage (removal of inflammatory cytokines, etc.) or disadvantage (removal of albumin, etc.) would depend on the condition of the patient.

The experimental model allowed clear identification of the times at which the TMP and $\Delta P_B$ began to rise, based on calculation of the dTMP/dt and $d\Delta P_B$ /dt, we considered that the time at which the TMP began to rise could be used as a marker of the time at which irreversible membrane pore fouling began to occur and the time at which the $\Delta P_B$ began to rise could be used as a marker of the time at which hollow fiber clogging began to occur. This may allow us to evaluate the mechanism of clogging by examining, for example, whether the pore fouling occurring first or the hollow fiber clogging occurred first, as well as the time difference between the start of these two events. We also considered that these times could be used as a measure of the membrane's potential to clog.

In the present study, 3 L of blood from one animal was divided into three parts for use in each of the three experiments, so that only 1 L of blood was circulated for a long time in each experiment. Therefore, comparisons among the three filters were possible in each experiment because blood from the same animal was divided into three portions. In addition, since we used an experimental system in which the filtrate was discarded and a substitution fluid was added to simulate a clinical situation, the total protein in the blood may have decreased, unlike in a clinical situation. Although there is some dissociation from the lifetime of the filter in clinical practice, this study was useful because it is impossible to treat the same patient with three different filters at the same time in a clinical situation.

Filter lifetime can be easily evaluated using this experimental model because the pressure rises rapidly. On the other hand, the pressure may rise slowly in clinical situations, and this model does not fully simulate clinical situations. In particular, since the blood volume in this model was relatively small, the protein level in the blood was expected to decrease faster, and the levels of coagulation factors likely decreased to a greater extent than that seen in clinical situations. Therefore, the lifetime obtained here may not be a meaningful value in itself. On the other hand, it was possible to compare three types of filters under the same conditions for a specific range of blood properties. The results of this study contain essential data for future filter development. The data obtained in this study are not a clinical indicator, but rather an in vitro evaluation of basic filter performance. From this perspective, we believe that we have obtained significant results.

Biocompatibility factors, such as platelet-related markers, were not measured in this study. Since the ease of hollow fiber clogging is also related to the activation of platelets and coagulation factors, changing the hollow fiber inner diameter and membrane area may also change the interaction of platelets and proteins with the PMMA membrane. Therefore, further examination of the effects of changes in membrane area and hollow fiber inner diameter from the viewpoint of biocompatibility is needed in future.

## Conclusions

We investigated how the filter lifetime and protein removal properties of PMMA membrane filters changed when the hollow fiber inner diameter and membrane area differed. An increase in membrane area from 1.0 to 1.8 $m^2$ contributed to the extension of the filter lifetime, while an increase in the hollow fiber inner diameter from 200 to 240 μm did not. On the other hand, the protein removal performance, especially the adsorption performance, was improved in the membranes with a larger hollow fiber inner diameter from 200 to 240 μm.

### Abbreviations

| | |
|---|---|
| PMMA | Polymethyl methacrylate |
| CRRT | Continuous renal replacement therapy |
| CHDF | Continuous hemodiafiltration |
| CHF | Continuous hemofiltration |
| $Q_B$ | Blood flow rate |
| $Q_S$ | Flow rate of the replacement fluid |
| $Q_F$ | Flow rate of filtrate |
| HCT | Hematocrit level |
| TP | Total protein concentration |
| $P_A$ | Arterial side pressure |
| TMP | Transmembrane pressure |
| $P_V$ | Venous side pressure |
| $P_F$ | Filtrate side pressure |
| $\Delta P_B$ | Pressure drop across the hemofilter |

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### Author contributions

YoKu designed the study, performed the experiment and data analysis, and wrote the manuscript; KeKo provided the working hypothesis, participated in the design of the study, and wrote the manuscript; YuKo, YU, and SU performed the experiment and data analysis; HT and KoKo participated in the design of the study and substantially contributed to the study's concept; MK and HK provided the working hypothesis, participated in the design of the study, and substantially contributed to the study concept.

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### Availability of data and materials

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

## Declarations

### Ethics approvaland consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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