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Permeability and secondary membrane formation of a high flux polysulfone hemofilter

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Permeability and secondary membrane formation of a high flux polysulfone hemofilter. It has been assumed that the molecular weight (MW) cut–off of a newly fabricated polysulfone capillary dialyzer (F60, Fresenius, FRG) is similar to that of the human glomerulus. We recently tested the device in vivo and found this not to be so, based on the device's ability to eliminate substances of a MW of 10,000 to 60,000 daltons. One of the reasons for this discrepancy was found to be the influence of secondary membrane formation on solute permeability. Endogenous marker substances of a defined MW (β_2-microglobulin, myoglobin, RBP, α_1-microglobulin, acid α_1-glycoprotein, α_1-antitrypsin, prealbumin, and albumin were measured by laser nephelometry or radioimmune assay; sieving coefficients (SC) and protein eliminations were calculated for each low MW protein.

During the first 10 min of hemofiltration the dialyzer was permeable to substances up to 66,000 daltons (albumin). Within 20 min the permeability decreased to less than 30,000 daltons, suggesting secondary membrane formation. Reuse with peracetic acid did not destroy the secondary membrane. Estimated albumin loss was 1.4 ± 0.7 g/20 liter filtrate with a new dialyzer and less than 0.5 g with a reused membrane. According to our studies, the in vivo cut–off of the polysulfone membrane is comparable to that of the peritoneum.

Survivals of more than 20 years have been achieved for patients on regular dialysis treatment (RDT). However, the rate of mortality and morbidity is high and the quality of life of patients on RDT is significantly less in comparison with renal transplantation [1, 2]. Hematologic, immunologic, dermatologic, neurologic, and metabolic alterations are observed in hemodialysis patients.

Middle molecular accumulation was suggested as a hypothetical explanation for these uremic symptoms seen in patients on conventional RDT, using cuprophane membranes with a cut–off of about 400–3,000 daltons [3–5]. However, results concerning the role of middle molecules in the pathogenesis of uremia is controversial [6]. Beyond the middle molecule range the functioning kidney filters substances up to 65,000 daltons and catabolizes low molecular weight (MW) proteins, peptides, and hormones [7, 8].

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For this reason, besides biocompatibility issues [10–13], new dialysis membranes have been developed. The polysulfone membrane is typical for a new generation of hemofilters which have high diffusive clearances for solutes of MW 60 to 5,000 as well as high sieving coefficients (SC) for larger MW substances, including small proteins [14]. The diffusive, convective, and mixed performance characteristics of this dialyzer for urea, creatinine, phosphate, insulin and β_2-microglobulin have been reported by Schneider and Streicher [15]. An SC of 0.79 for β_2-microglobulin was calculated for convective transport. The aim of this study was to test this device for its ability to remove possibly toxic substances of the higher MW range. Special consideration was given to the effects of reuse and secondary membrane formation.

Methods

Studies were performed on six patients on RDT (four male, two female; aged 58.8 ± 9.8 years; time on dialysis 46.2 ± 28.3 months; three with polycystic disease, two with chronic glomerulonephritis, one with diabetic glomerulopathy). A polysulfone capillary dialyzer (Hemoflow F60, Fresenius, FRG) was tested during first use and third reuse. At the beginning and the end of their dialysis treatment patients were put on filtration for 20 and 10 minutes, respectively.

During filtration, the mean ultrafiltration rate (UFR) was 55 ml/min with a new membrane (38 ml/min with a reused membrane), mean transmembraneous pressure (TMP) was 160 mm Hg (200 mm Hg with reuse), and blood flow was constant at 200 ml/min. The monitor used was the MTS 2008 (Fresenius, FRG). For reuse, the capillaries were prepared with an automated system (Renatron, Renal Systems Inc., Minneapolis, Minnesota USA) using peracetic acid (Acetoper 2000, Bionic, FRG) as a cleansing and sterilizing agent. The main criteria for the quality control of reused dialyzers were: at least 80% of original fiber volume, few visible deposits, and a passed pressure test.

Patients' serum samples were obtained at time 0 (Cb 0) and 180 minutes (Cb 180); ultrafiltrate samples were taken at time 0, 30, 60, 90 seconds and 2, 5, 10, 20, 180 minutes after the start of treatment. Samples were stored in fractions in polyethylene tubes at a temperature of −70°C and thawed only once for analysis. The marker substances albumin (66,290 daltons), prealbumin (54,900 daltons), α_1-antitrypsin (54,000 daltons), acid α_1-glycoprotein (41,000), α_1-microglobulin (26,700 daltons), and retinol–binding–protein (RBP) (21,000 daltons) were

Table 1. Peak sieving coefficients (PSC) and sieving coefficients at 20 min (SC 20) and 180 min (SC 180) of low MW proteins ($\bar{X}$ ± SEM) during hemofiltration with new and reused dialyzers[a]

Protein	SC	First use	Reuse
β_2-microglobulin	PSC	0.76 ± 0.03	0.58 ± 0.02
(11,818 daltons)	SC 20	0.60 ± 0.02*	0.58 ± 0.02
	SC 180	0.52 ± 0.03*	0.49 ± 0.02*
Myoglobin	PSC	0.25 ± 0.03	0.06 ± 0.01
(17,200 daltons)	SC 20	0.11 ± 0.02*	0.06 ± 0.01*
	SC 180	0.11 ± 0.01*	0.04 ± 0.01*+
Retinol–binding	PSC	0.09 ± 0.01	0.01 ± 0.01
protein	SC 20	0.04 ± 0.01*	0.01 ± 0.01+
(21,000 daltons)	SC 180	0.03 ± 0.01*	0.01 ± 0.01+
α_1–microglobulin	PSC	0.10 ± 0.01	0.01 ± 0.01
(26,700 daltons)	SC 20	0.01 ± 0.01	0.01 ± 0.01
	SC 180	0.01 ± 0.01*	0.01 ± 0.01
α_1-glycoprotein	PSC	0.05 ± 0.01	<0.01
(41,000 daltons)	SC 20	<0.01*	<0.01
	SC 180	<0.01*	<0.01
α_1-antitrypsin	PSC	0.03 ± 0.01	<0.01
(54,000 daltons)	SC 20	<0.01*	<0.01
	SC 180	<0.01*	<0.01
Prealbumin	PSC	<0.01	<0.01
(54,980 daltons)	SC 20	<0.01	<0.01
	SC 180	<0.01	<0.01
Albumin	PSC	0.02 ± 0.01	<0.01
(66,290 daltons)	SC 20	<0.01	<0.01
	SC 180	<0.01	<0.01

[a] Significances ($P < 0.05$) between PSC and SC 20, SC 180 (*), and between SC 20, SC 180 in first used and reused membranes (+) were tested.

analysed by laser nephelometry using rabbit antisera (Behring, FRG). Myoglobin (17,200 daltons, Mallinckrodt, FRG) and β_2-microglobulin (11,818 daltons, Pharmacia, Uppsala, Sweden) were determined by radioimmune assay. For the evaluation of membrane permeability, the sieving coefficients (SC) were calculated using the concentration in the afferent blood line (Cb) and in the ultrafiltrate (Cf) according to the following formula:

$$SC = \frac{Cf}{Cb}$$

For calculation of SCs during the first 20 minutes Cb 0, for the three hour SCs, Cb 180 was used. Significances were calculated using the Wilcoxon ranked sum test. Protein elimination was estimated by calculating the area under curve (protein concentration versus ultrafiltrate flow). For comparison with a hemofiltration therapy the values were computed in mg/20 liter ultrafiltrate.

Results

Table 1 shows the peak sieving coefficients (PSC) and sieving coefficients at 20 min (SC 20) and 180 min (SC 180) after the start of ultrafiltration using new and reused membranes. During the first 10 min of treatment, the new membrane was permeable to substances of a MW up to 66,290 daltons (albumin); The higher the MW of substances was, the lower was their PSC (0.76 ± 0.06 for β_2-microglobulin, 0.02 ± 0.01 for albumin). Twenty min after the start of ultrafiltration, the permeability had decreased significantly ($P < 0.05$); thereafter only substances of less than 30,000 daltons were filtered. The higher the MW of substances was, the stronger was their decrease of SCs during the first 20 min (21% decrease for β_2-microglobulin, 60% decrease for α_1-antitrypsin). Reused membranes were significantly less permeable to myoglobin and RBP than new ones; they showed no decline of permeability during dialysis.

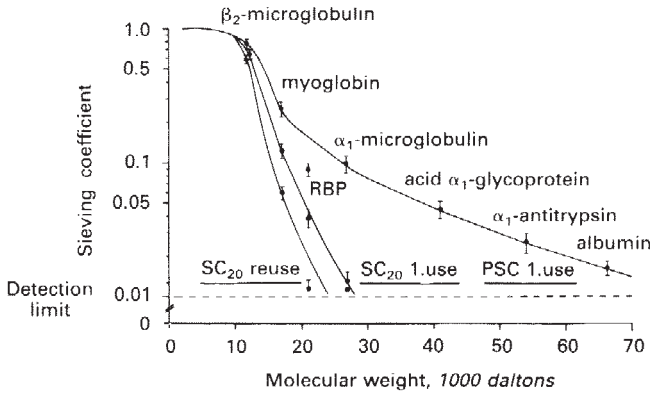

Fig. 1. *Peak sieving coefficients ($\bar{X}$ ± SEM) of low MW proteins and SC after 20 min of hemofiltration with first used, and then reused F60 polysulfone capillary dialyzers.*

Figure 1 shows the PSC and SC 20 of new membranes in comparison the SC 20 of reprocessed dialyzers.

Figure 2 shows the SCs of each low MW protein during the time course of hemofiltration comparing new and reused membranes. The values of prealbumin and retinol–binding–protein (RBP) were excluded from this curve since their SCs were falsely low, probably due to their high plasma protein binding. The three proteins with a MW of more than 40,000 daltons (albumin, α_1-antitrypsin, and acid α_1-glycoprotein) had a PSC of less than 0.05 with a new and less than 0.01 with a reused dialyzer. They became undetectable in the ultrafiltrate after the first few minutes of treatment. α_1-microglobulin (26,700 daltons) had a PSC of less than 0.10 with first use and less than 0.01 with reuse. It was the largest protein detectable at 180 min of both first use and reuse filtration.

Figures 2 and 3 show the correlation between the time of maximum permeability (PSC) and the MW of each plasma protein; the higher the MW of a substance was, the earlier the PSC occurred and the faster did the SC decrease.

Table 2 lists the calculated losses for each low MW protein based on a ultrafiltrate volume of 20 liter. During first use and reuse hemofiltration the calculated albumin loss was 1.4 g and less than 0.5 g, respectively.

Discussion

Protein and fibrin layer a deposit on membrane surfaces after blood contact during hemodialysis, forming a secondary membrane [16]. The consequence is a decrease of ultrafiltration rate and permeability, especially to substances of a MW greater than 5,000 daltons [17–19]. Because of the in vivo formation of secondary membranes, in vitro studies using dextranes of different molecular weights in aqueous solutions may be inadequate to investigate permeability properties of hemodialysis membranes.

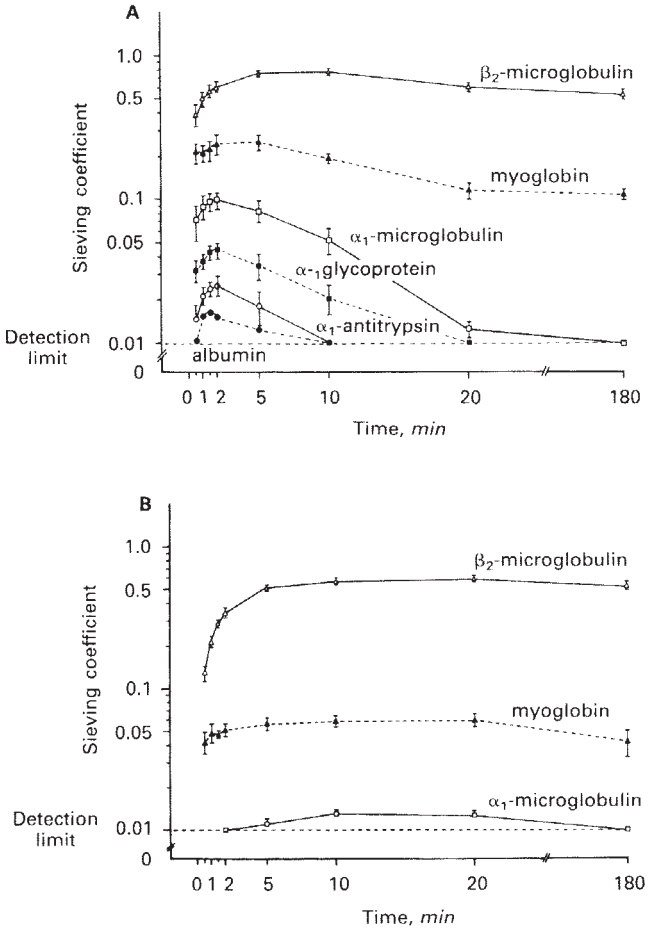

Fig. 2. *Sieving coefficients ($\bar{X}$ ± SEM) of low MW proteins during hemofiltration with first used (A), and then reused (B) F60 polysulfone hemodialyzers.*

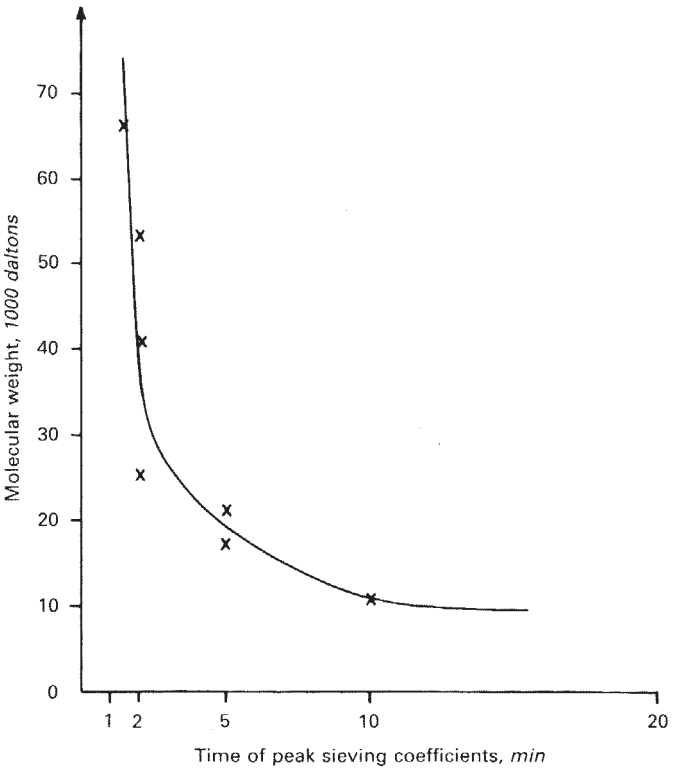

Fig. 3. *Relationship between the MW of plasma proteins and the time of their peak sieving coefficients during hemofiltration with first used F60 polysulfone hemodialyzers.*

Table 2. Calculated loss of plasma proteins ($\bar{X}$ ± SEM) during a 20 liters hemofiltration, comparing new and reused dialyzers.

Protein	First use loss	Third reuse loss
β_2-microglobulin	240 ± 18	235 ± 10
Myoglobin	465 ± 103	224 ± 26
Retinol–binding protein	145 ± 17	38 ± 3
α_1-microglobulin	80 ± 11	36 ± 4
α_1-glycoprotein	162 ± 40	<25
α_1-antitrypsin	117 ± 32	24 ± 3
Prealbumin	22 ± 2	<18
Albumin	1382 ± 269	500

It was already shown that the protein adsorption on polysulfone did not alter the membrane permeability for small and middle molecular substances [14, 17]. The hyperbolic shape of the curve in Figure 3 confirms these findings. The secondary membrane seems to influence the permeability of substances up to a certain MW only. The lower the MW of a substance, the lesser the influence of the secondary membrane on its permeability.

We evaluated membrane permeability characteristics during the course of hemofiltration using endogenous marker substances with a defined MW between 11,800 and 66,200 daltons. Under the prescribed conditions, the new polysulfone membrane was well permeable for β_2-microglobulin and myoglobin throughout the treatment period. In the higher MW range (above 40,000 daltons), the permeability was low (SC < 0.05) before and neglegible after secondary membrane formation, which we found to be completed within 20 min after the start of treatment.

This membrane was reported to have a cut–off comparable to that of the glomerulus [20, 21]. We found similar results at the start of dialysis. However, taking into account the secondary membrane formation, our findings demonstrate in vivo permeability characteristics of this membrane to be similar to those of the peritoneum [22, 23].

An important requirement in chronic high flux hemodialysis treatment is the limitation of protein loss. This is nearly fulfilled with an estimated albumin loss of only 1.4 g/20 liters filtrate with first use and less than 0.5 g with reuse. The albumin loss during the first use may be further minimized by using slow blood flow, low TMP and UFR during the first 10 to 20 min of treatment until secondary membrane formation is complete. This procedure is not necessary with a reused membrane since peracetic acid does not destroy the secondary membrane. However, dialysing at a low TMP and low UFR may result in backfiltration [24] with consequent influx of LAL-positive substances [25]. These arguments might refute the recommendation for membranes with even greater permeability.

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