Dialytic performance evaluation of Rexeed™: A new polysulfone-based dialyzer with improved flow distributions

A. BRENDOLAN, F. NALESSO, A. FORTUNATO, C. CREPALDI, M. DE CAL, S. CAZZAVILLAN, D. CRUZ, N. TECHAWATHANAWANNA, C. RONCO

Departments of Nephrology, Pathology and Biochemistry, St. Bortolo Hospital, Vicenza - Italy

Reprinted from

THE INTERNATIONAL JOURNAL OF ARTIFICIAL ORGANS

Vol. 28, no. 10, 2005 - pp. 966-975

WICHTIG EDITORE
MEDICAL PUBLISHER

Artificial Kidney and Dialysis

Dialytic performance evaluation of Rexeed™: A new polysulfone-based dialyzer with improved flow distributions

A. BRENDOLAN, F. NALESSO, A. FORTUNATO, C. CREPALDI, M. DE CAL, S. CAZZAVILLAN, D. CRUZ, N. TECHAWATHANAWANNA, C. RONCO

Departments of Nephrology, Pathology and Biochemistry, St. Bortolo Hospital, Vicenza - Italy

ABSTRACT: New dialyzers are designed to optimize the convective and diffusive components of solute transport. Asahi Kasei Medical Co., Ltd. has developed a new high flux dialyzer series called Rexeed™ with improved flow distributions. We evaluated the in vivo dialytic performance of two dialyzers of the Rexeed™ series: Rexeed-18A and Rexeed-25A (1.8 m^2 and 2.5 m^2).

We calculated the clearance for urea, creatinine, phosphate and b2-microglobulin both in high flux dialysis (HFD) and in 15 liter postidiluitional on-line hemodiafiltration (HDF) mode.

With n=3 patients in high flux HD at blood flow 450, 400, 350 and 250 ml/min we found remarkably high clearance for urea (347±4%,305±0%,288±5%,230±3%, for Rexeed-18A and 361±3%,329±0%,313±1%,234±3% for Rexeed-25A), creatinine (282±10%,234±0%, 221±8%, 174±8%, for Rexeed-18A and 276±6%,245±0%,226±9%,172±13% for Rexeed-25A), phosphate (347±0%,316±0%,275±4%,202±16%, for Rexeed-18A and 364±3%,365±0%,286±3%,224±2% for Rexeed-25A) and b2-microglobulin (133±21%,124±0%,118±12%,98±11%, for Rexeed-18A and 159±8%,169±0%,157±8%,129±7% for Rexeed-25A)

With n=2 patients in HDF at blood flow 300 ml/min we found remarkably high clearance for urea (268±2%, for Rexeed-18A and 283±2% for Rexeed-25A), creatinine (183±6% for Rexeed-18A and 205±9% for Rexeed-25A), phosphate (245±3%, for Rexeed-18A and 270±2% for Rexeed-25A) and b2-microglobulin (166±12%, for Rexeed-18A and 192±4% for Rexeed-25A).

Our preliminary evaluation describes the characteristics and the performances of a new polysulfone-based hemodialyzer series called Rexeed™. Several innovative features have been implemented by the manufacturer. These constructive approaches seem to have produced a positive effect on the dialyzer performance at the bedside. (Int J Artif Organs 2005; 28: 966-75)

KEY WORDS: Hemodialyzer clearance, Polysulfone, Dialysate flow distribution, Hemodialyzer design

INTRODUCTION

Thanks to the accuracy reached by new dialysis machines on ultrafiltation control and to the high purity of on-site prepared bicarbonate dialysate, the use of high flux dialyzers is progressively increasing. The high hydraulic permeability of these devices permits the removal of solutes in a range wider than that obtained with low flux membrane; this characteristic has been suggested to possibly improve clinical outcomes especially in terms of comorbidity of dialysis patients.

Recently Asahi Kasei Medical Co., Ltd. developed a new dialyzer series called Rexeed™ with a new high flux polysulfone-based membrane called Rexbrane™, an evolution of the previous Asahi Polysulfone™ APS. The new dialyzers present a modified flow geometry which combines very efficiently diffusion and convection in the attempt to obtain high clearances either in HFD (high flux dialysis) or in HDF (hemodiafiltration).

0391-3988/966-10 $15.00/0

In this study we describe the characteristics and the *in vivo* performance of two Rexeed™ models: Rexeed-18A and Rexeed-25A with respectively 1.8 m^2 and 2.5 m^2 active surface area.

The evaluation was carried out under different conditions of ultrafiltration and blood flow rates in patients with different Ht%. In particular, the filters were tested for solute clearances and hydraulic permeability under conditions of hemodialysis (defined as HFD or high flux dialysis, since we are dealing with a high flux membrane) and hemodiafiltration (HDF).

The assessment was completed with a study on beta-2-microglobulin clearance and percent reduction.

METHODS

Clearance studies were performed in hemodialysis and hemodiafiltration sessions (18 sessions) at various blood flows according to a previously described technique (1, 2).

The hemodialysis session

Rexeed-18A (1.8 m^2) and Rexeed-25A (2.5 m^2) dialyzers were tested in conditions of hemodialysis carried out with dialysis machines equipped with ultrafiltration control and on site preparation of bicarbonate dialysate (3). Considering the high ultrafiltration coefficient of the membrane and the relatively low scheduled weight loss for the patients, the treatment should be defined as high flux dialysis. At the rate of ultrafiltration scheduled and at the set blood flows, a certain amount of backfiltration is inevitable. Thus the amount of convection present is certainly exceeding the amount of net ultrafiltration observed during treatment (4-15).

Clearances studies were performed after calibration of the blood pump at 250, 350 and 450 ml/min of blood flow. Dialysate flow rate was set at 500 ml/min. Ultrafiltration was maintained equal to the scheduled patient's weight loss.

Clearances were determined for urea, creatinine, phosphate and beta-2-microglobulin. Pre and post dialysis values were also measured for urea to calculate equilibrated Kt/V. The post dialysis sample was taken 15 minutes after the end of the session. Clearance calculation was made both in the blood and the dialysate side thus permitting mass balance error calculation. In each session, the hematocrit value was measured enabling the calculation of plasma flow rate from the set blood flow. The blood side clearance was measured utilizing the following formula:

$$K = [(Qbi*Cbi) - (Qbo*Cbo)] / Cbi$$

while the dialysate side clearance was measured utilizing the formula

$$K = Qd*Cdo$$

where K is clearance, Qbi is inlet blood flow, Qbo is outlet blood flow, Cbi is the concentration of the solute in the arterial line, Cbo is the concentration of the solute in the venous line and Cdo is the concentration of the solute in the spent dialysate. Qbo was obtained by the difference between Qbi and ultrafiltration (Qf). For the calculation of clearance for solutes confined to plasma water, plasma flow was used instead of blood flow.

The data were collected in a flow chart (excel format) in which the following information was reported: Type of dialyzer, patient initials, dialysis schedule (hemodialysis = HFD), presence of ultrafiltration control (Contr UF), treatment duration (duration in minutes), total weight loss in mg, total ultrafiltration in mL (Total UF), reinfusion in mL, blood flow (Qb), dialysate flow (Qd), net ultrafiltration rate in ml/min (Qf), hematocrit (Ht).

For each solute clearance study the following data were collected:

Concentration in the arterial line (A), concentration in the venous line (V), concentration in spent dialysate (LD), volume of spent dialysate collected in the period t (VD), time of collection of spent dialysate in minutes (t= 10 minutes), dialysate flow rate (Qd).

Urea concentrations before and after the session to calculate Kt/V with the Lowrie formula (16-25). Kt/V was calculated in a specific session with the usual prescription for every studied patient.

The hemodiafiltration session

Rexeed-18A and Rexeed-25A dialyzers were tested in conditions of online-hemodiafiltration carried out with dialysis machines equipped with ultrafiltration control and on site preparation of bicarbonate dialysate. Fluid reinfusion (average 15 liters per session) was delivered by a pump in postdilutional mode according to the programmed ultrafiltration and patient weight loss.

Clearances studies were performed at 300 ml/min blood flow. Fifteen liters of reinfusion were programmed in each session, and the total amount of ultrafiltration was calculated by the sum of the reinfusion and the required patient weight loss.

Clearances were determined for urea, creatinine, phosphate and beta-2-microglobulin. Pre and post dialysis values were also measured for urea. Clearance calculation was made both in the blood and the dialysate side thus permitting mass balance errors calculation. In each session, the hematocrit value was measured enabling the calculation of plasma flow rate from the set blood flow.

CONDUCTION OF THE SESSIONS

All sessions were recorded in terms of behavior of ultrafiltration over time, and transmembrane pressure measurements along the length of the treatment (26-36).

In all sessions patient well being and possible adverse reactions were recorded in a special flowchart.

The final aspect of the dialyzer was analyzed after rinsing the filter with saline solution and restituting the blood to the patient. The external aspect of the fibers and of the blood ports was carefully examined.

RESULTS

No adverse reactions were observed during the study and all the dialysis sessions were well tolerated from the clinical point of view.

The dialyzers displayed a clean aspect at the end of the session demonstrating a minimal blood rest within the fibers.

The amount of heparin used for the study was exactly the same utilized by the patients during their regular hemodialysis treatment.

Just slight variations of the transmembrane pressure throughout the sessions were observed, demonstrating a constant performance of the hydraulic permeability of the membrane.

Hemodialysis sessions

We treated n=3 patients both with Rexeed-18A (1.8 m^2) and with Rexeed-25A (2.5 m^2).

The Ht=39±11% and the session duration was 225±16% minutes.

In one patient it was not possible to reach 450 ml/min of constant blood flow due to fistula characteristics, so we calibrated the blood pump at 400 ml/min.

Remarkable clearances for the various molecules were obtained with the Rexeed™ dialyzers both as absolute values and as a comparison with other dialyzers in the similar range of surface area. The clearances tend to remain stable throughout the entire duration of the session. Particularly high clearances for phosphate were found, even comparable with those of urea. Equilibrated KT/V was particularly satisfying with mean value of 1.2±9% in 226±16% minutes of dialysis with an average blood flow of 300 ml/min, especially using the biggest surface (2.5 m^2) (Tab. I).

The hemodiafiltration sessions

We treated n=2 patients both with Rexeed-18A (1,8 m^2) and with Rexeed-25A (2,5 m^2). The Ht=38±7% and the session duration was 226±13% minutes. In both patients clearances were measured at 300 ml/min.

Compared to hemodialysis the clearances of the larger solutes were significantly affected by the higher amount of convection achieved in hemodiafiltration. The larger surface area of the Rexeed-25A always played an important role in increasing the solute clearances. High clearances for low molecular weight solutes were found, comparable to those found during HFD. Equilibrated KT/V reached a value of 1.1±1,4% in 226±13% minutes of HDF at an average blood flow of 300 ml/min. The clearances tended to remain stable over the entire duration of the dialysis session (Tab. II).

Beta-2 microglobulin study

The clearances resulted remarkably high both in hemodialysis and in hemodiafiltration. The impact of dialyzer surface area is evident as well. The positive effect of high convective rates is demonstrated by the better results achieved in hemodiafiltration. The membrane therefore seems adequate to achieve significant removals of beta-2-microglobulin during both hemodialysis and hemodiafiltration.

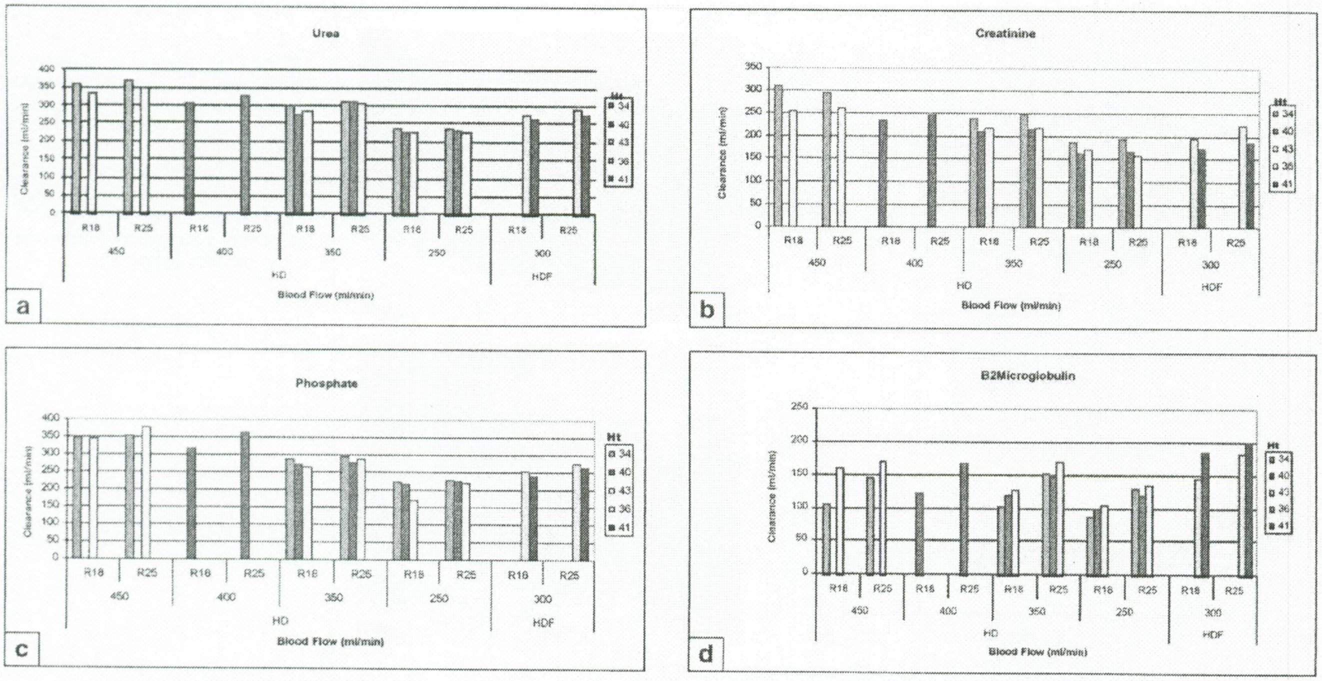

Fig. 1 - **(a)** *Urea clearances;* **(b)** *Creatinine clearances;* **(c)** *Phosphate clearances;* **(d)** *Beta-2 microglobulin clearances.*

From the results it appears evident that the significant removal obtained with Rexeed™ dialyzers is due to the substantial amount of filtration during treatment.

The clearance data are reported graphically in Figures 1a-d.

TABLE I - MEAN VALUES OF CLEARANCES OF DIFFERENT SOLUTES MEASURED DURING HIGH FLUX DIALYSIS SESSION

Rexeed 18 A												
	HD								KT/V		Time (min)	
Qb(ml/min)	450		400		350		250					
Solute	K (ml/min)	± %	K (ml/min)	± %	K (ml/min)	± %	K (ml/min)	± %		± %		± %
Urea	347	4	305	0	288	5	230	3				
Creatinine	282	10	234	0	221	8	174	8	1.2		225	
Phosphate	347	0	316	0	275	4	202	16		8		18
B2-microglobulin	133	21	124	0	118	12	98	11				

Rexeed 18 A												
	HD								KT/V		Time (min)	
Qb(ml/min)	450		400		350		250					
Solute	K (ml/min)	± %	K (ml/min)	± %	K (ml/min)	± %	K (ml/min)	± %		± %		± %
Urea	361	3	329	0	313	1	234	3				
Creatinine	276	6	245	0	226	9	172	13	1.2		225	
Fosfati	364	3	365	0	286	3	224	2		12		18
B2-microglobulin	159	8	169	0	157	8	129	7				

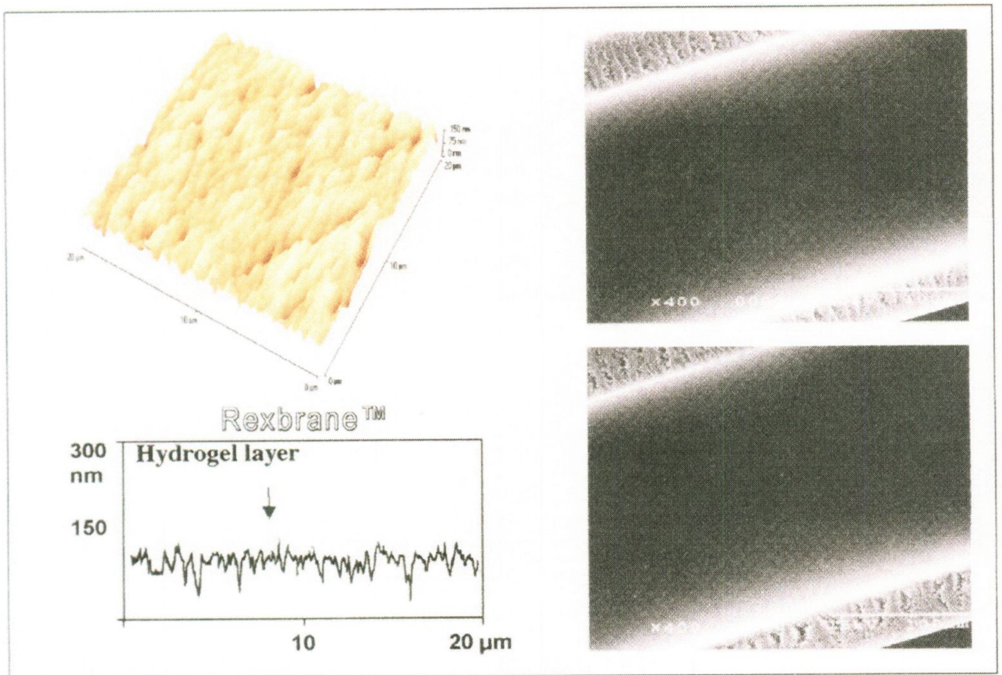

Fig. 2 - On the left panel AFM micrograph shows the hydrogel layer on surface of Rexbrane™. The SEM micrographs depict the inner surface of a fiber of Rexbrane™ after hemodialysis session in arterial (upper) and venous (lower) side of the blood compartment (Courtesy of Asahi). The surfaces are clean with very low protein adsorbtion.

DISCUSSION

Dialyzer characteristics

From the results achieved and from the analysis of the structure of the dialyzers studied we might speculate that the manufacturer's efforts were focused on enhancing the performance by exploiting the properties of the high flux membrane in conjunction with new flow geometry characteristics. The design aims at maximizing both diffusive and convective exchanges optimizing the performance of every fiber in the bundle.

Rexbrane™ is characterized by a high hydraulic permeability that allows the use of Rexeed™ dialyzers in high flux dialysis or in more sophisticated convective techniques such as on-line HDF (ultrafiltration coefficient for the Rexeed 18 A is Kf=71 ml/h/ mmHg and Rexeed 25 A Kf=80 ml/h/mmHg).

The membrane is appropriately made of a copolymer of polysulfone and polyvinylpirrolidone that gathers hydrophobic and hydrophilic properties of the two different monomers to obtain biocompatibility on a specific microdomain surface.

In fact the chemical nature of membrane surface strongly affects the interactions with blood components. The simultaneous presence of hydrophobic-hydrophilic domains on the surface of Rexbrane™ permits the formation of a few nanometers thick hydrogel layer that drastically reduces the thrombogenicity and protein adsorption (Fig. 1).

Nevertheless the entire contribution of the polysulfone material to biocompatibility is its very low complement activation.

The combination of these different characteristics results in very high biocompatibility, at least comparable with most biocompatible polysulfone-based membranes (Fig. 2).

The biocompatibility of this membrane is guaranteed by its homogenously porous asymmetric thickness structure (Fig. 3) depicted in the membrane micrograph. This has been shown to constitute an efficient barrier against endotoxin passage from dialysate to the blood compartment (37).

Concentrating on the dialyzer (Fig. 4) design, the header is larger than usual and the blood pressure at the inlet can be distributed over a wider surface, so the blood flows through the fiber bundle smoothly and homogenously, reducing the blood stress in the potting area.

Also the inner profiles of the housing have been specifically designed to obtain the most homogenous dialysate flow possible.

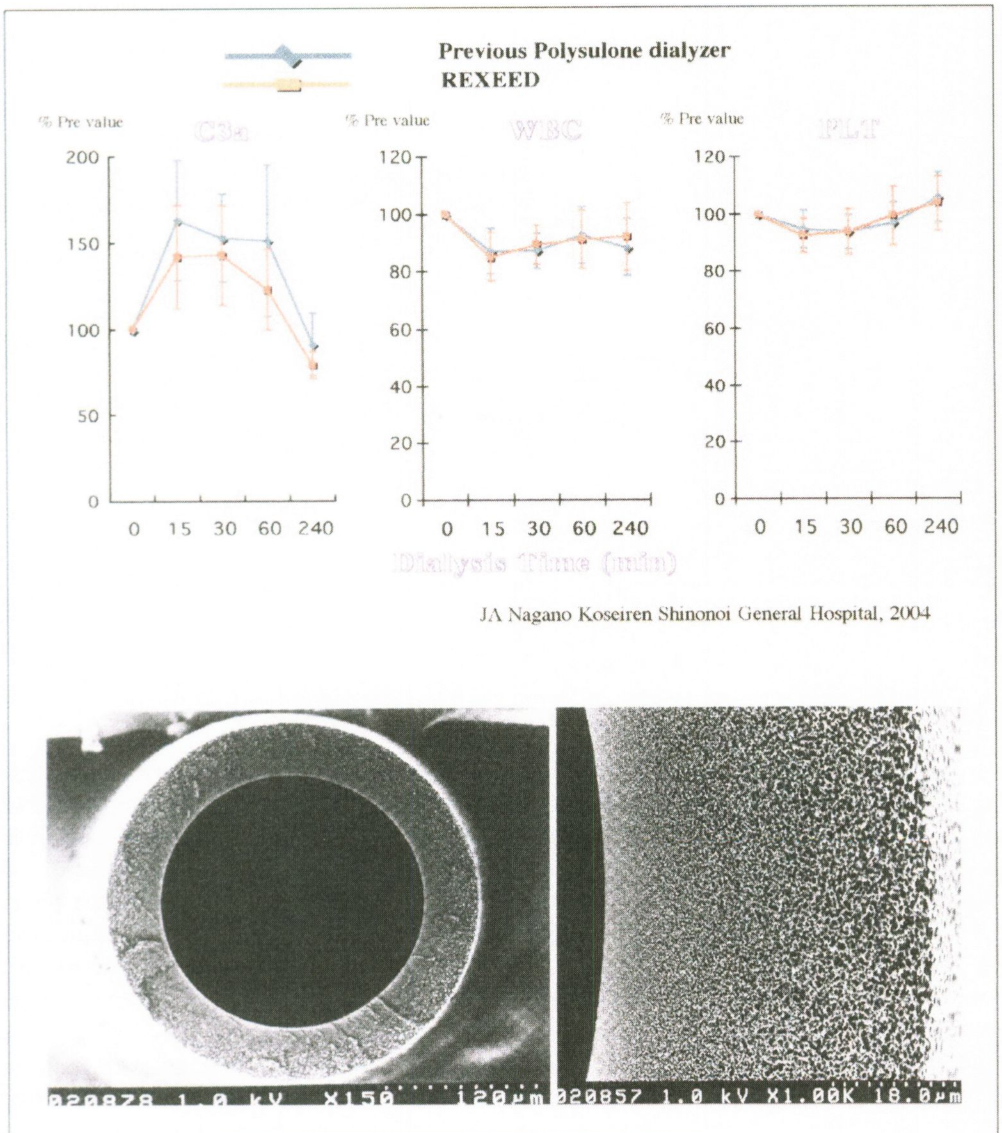

Fig. 3 - *Upper panel: Biocompatibility test performed in Japan (Courtesy of Asahi). Lower panel: The SEM micrographs show the microporous structure of the fibers (Courtesy of Asahi).*

At the inlet port, the dialysate is distributed in all radial directions thanks to a baffle panel (Figs. 4, 5 and 6), while the housing profiles permit smooth pressure distributions so that the dialysate flows within the whole transversal section of the dialyzer as homogeneously as possible.

Thanks to waving fibers the homogenous distribution of the dialysate at the inlet port is still maintained along the length of the dialyzer.

The induced spacing between fibers permits a constant flushing of the whole external surface of fibers by fresh dialysate, better exploiting the whole exchange surface provided by the fiber bundle.

From this analysis of the dialyzer structure, we can conclude that Rexeed™ series embodies state-of-the-art dialyzer manufacturing.

Dialyzer performance

Figure 1 (a-d) shows that the Rexeed™ dialyzers maintain high clearance performance through a wide range of Ht.

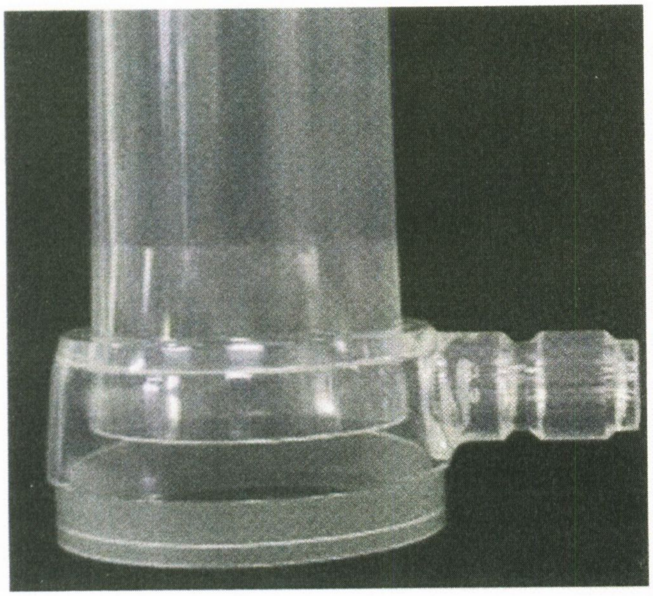

Fig. 4 - *The new design of the blood ports, with large surface, new profiles and baffle panel (Courtesy of Asahi).*

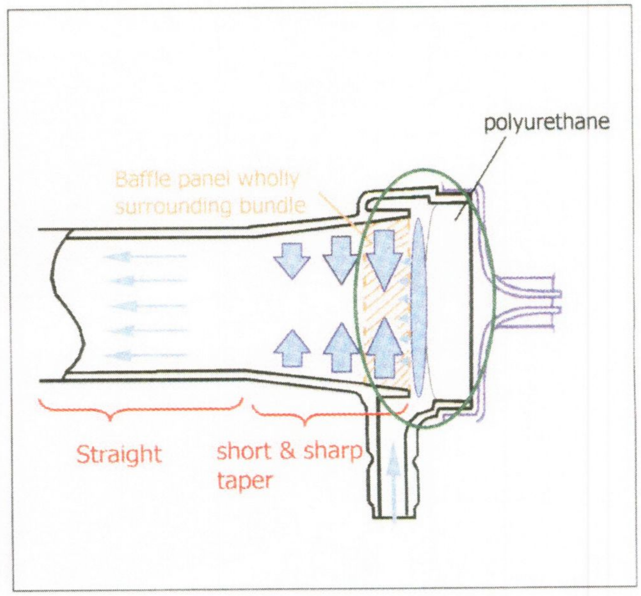

Fig. 5 - *The new dialysate distribution in the dialysate compartment (Courtesy of Asahi).*

This could be achieved thanks to the good flow distribution in the blood and dialysate compartments derived from its accurate design.

TABLE II - MEAN VALUES OF CLEARANCES OF DIFFERENT SOLUTES MEASURED DURING HEMODIAFILTRATION IN POST DILUTIONAL MODE (15 LITERS)

Rexeed 18 A						
HDF			KT/V		Time (min)	
Qb(ml/min)	300					
Solute	K (ml/min)	± %		± %		± %
Urea	268	2				
Creatinine	183	6	1.1		228	
Phosphate	245	3		10		20
B2-microglobulin	166	12				
Rexeed 25 A						
HDF			KT/V		Time (min)	
Qb(ml/min)	300					
Solute	K (ml/min)	± %		± %		± %
Urea	283	2				
Creatinina	205	9	1.1		225	
Phosphate	270	2		13		9
B2-microglobulin	192	4				

The figures also show that the clearance of low molecular solutes in HDF are comparable with those in HFD, confirming that the new dialysate distribution is efficient in combining diffusive and convective fluxes.

In fact fresh dialysate can homogenously wet the whole surface provided by the fiber bundles, maximizing concentration gradients (diffusive mechanism) and improving the pressure profiles along the dialyzer length (convective mechanism).

Moreover, the very high phosphate clearance, both in high flux dialysis and in HDF, could represent an important clinical indication for this kind of dialyzer in relation to Malnutrition Inflammation Atherosclerosis (MIA) syndrome.

Rexeed™ show very high values of beta-2 microglobulin clearance in both modalities, confirming how high flux membranes can efficiently remove a wider range of solutes than low flux membranes even in high flux dialysis.

It is evident from the figure that techniques with a high amount of ultrafiltration such as HDF can dramatically improve the removal of middle molecules thanks to convective transport. In these circumstances, the contribution of a larger surface area is more evident than ever.

In conclusion, our preliminary evaluation describes the characteristics and the performance of a new

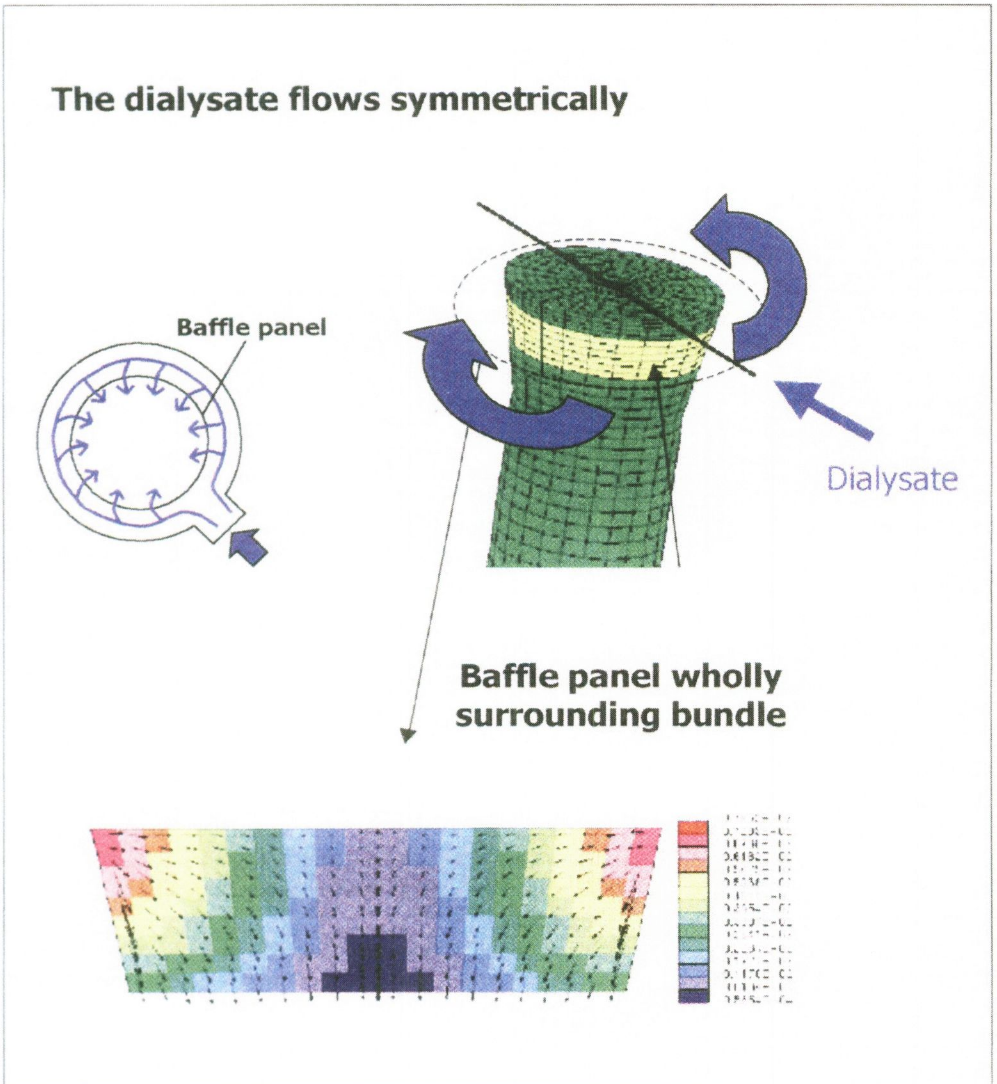

Fig. 6 - *Pressure distribution on dialysate compartement (Courtesy of Asahi).*

polysulfone-based hemodialyzer series. Several innovative features have been implemented by the manufacturer. These constructive approaches seem to have produced a positive effect on the dialyzer performance at the bedside.

ACKNOWLEDGEMENTS

We would like to thank Andrea Scabardi for his assistance, collection of the experimental data and the preparation of the manuscript.

Address for correspondence:
Alessandra Brendolan, MD
Divisione di Nefrologia
Ospedale San Bortolo
Via Rodolfi
36100 Vicenza, Italy
e-mail: Alessandra.brendolan@ulssvicenza.it

REFERENCES

1. Ronco C, Fabris A, Chiaramonte S, De Dominicis E, Feriani M, Brendolan A, Bragantini L, Milan M, Dell'Aquila R, La Greca G. Comparison of four different short hemodialysis techniques. Int J Artif Organs 1988; 3: 169-74.
2. Ronco C, Fabris A, Chiaramonte S, De Dominicis E, Feriani M, Brendolan A, Bragantini L, Milan M, Dell'Aquila R, La Greca G. Impact of high blood flows on vascular stability in hemodialysis. Nephrol Dial Transplant 1990; 1 (suppl 5): S109-14.
3. Tolchin DO. Acetate metabolism and high efficiency hemodialysis. Int J Artif Organs 1979; 2: 1-6.
4. Ronco C, Fabris A, Feriani M, Chiaramonte S, Brendolan A, Bragantini L, Milan M, Dell'Aquila R, Conz P, Frigato G, Borra M, von Albertini B, La Greca G. Technical and clinical evaluation of a new system for ultrafiltration control during hemodialysis. Trans Am Soc Artif Intern Organs 1988; 3: 613-5.
5. Bosch JP, von Albertini B, Ronco C. Hemofiltration and Hemodiafiltration. In: Glassock RJ, ed. Current therapy in nephrology and hypertension 2. Toronto-Philadelphia: BC Decker Inc; 1987. p 258-63.
6. Santoro A, Spongano M, Ferrari G, Zucchelli P. Analysis of the factors influencing bicarbonate balance during acetate free biofiltration. Kidney Int 1993; 43 (suppl 41): S184-7.
7. Ghezzi PM, Frigato G, Fantini GF, et al. Theoretical model and first clinical results of the paired filtration dialysis. Life Support Syst 1983; (suppl 1): S271-4.
8. Feriani M, Ronco C, Biasioli S, Bragantini L, La Greca G. Effect of dialysate and substitution fluid buffer on buffer flux in hemodiafiltration. Kidney Int 1991; 39: 711-7.
9. Canaud B, Imbert E, Kaaki M, Assounga A, Nguyen QV, Stec F, Garred LJ, Bostrom M, Mion C. Clinical and microbiological evaluation of a postdilutional hemofiltration system with inline production of substitution fluid. Blood Purif 1990; 8: 160-70.
10. Ronco C. Backfiltration in clinical dialysis: Nature of the phenomenon, mechanisms and possible solutions. Int J Artif Organs 1990; 13: 11-21.
11. Ronco C, Brendolan A, Crepaldi C. Water and dialysate treatment for hemodialysis. In: Bosch JP, ed. Hemodialysis; high efficiency treatments. New York: Churchill Livingstone; 1993. p 41-61.
12. Ronco C, Ghezzi PM, Brendolan A, Crepaldi C, La Greca G. The haemodialysis system: Basic mechanism of water and solute transport in extracorporeal renal replacement therapies. Nephrol Dial Transplant, 1998; 13 (suppl 6): S3-9.
13. Brendolan A, Ronco C, Ghezzi PM, Scabardi M, La Greca G. Hydraulic and flow-dynamic characteristics of PMMA dialyzers. Contrib Nephrol 1998; 125: 41-52.
14. Ronco C, Scabardi M, Goldoni M, Brendolan A, Crepaldi C, La Greca G. Impact of spacing filaments external to hollow fibers on dialysate flow distribution and dialyzer performance. Int J Artif Organs 1997; 20: 261-6.
15. Ronco C, Orlandini G, Brendolan A, Lupi A, La Greca G. Enhancement of convective transport by internal filtration in a modified experimental hemodialyzer. Kidney Int 1998; 54: 979-85.
16. Lowrie EG, Laird NM, Parker TF, Sargent JA. Effect on the hemodialysis prescription on patient morbidity. N Engl J Med 1981; 20: 1176-81.
17. U.S. Renal Data System. USRDS 1991 Annual Data Report. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. 1991: p D.1-E.62.
18. Acchiardo SR, Hatten KW, Ruvinsky MS, Dyson B, Fuller J, Moore LW. Inadequate dialysis increases gross mortality rate. ASAIO J 1992; 38: M282-5.
19. Levin NW, Gotch FA, Daugirdas JT, Teschan PE, Collins AJ, Keshaviah P. What is the role of Kt/V urea in chronic dialysis. Semin Dial 1990; 3: 73-4.
20. Jindal KK, Manuel A, Goldstein MB. Percent reduction of the blood urea concentration during hemodialysis (PRU), a simple and accurate method of estimate Kt/V urea. Trans Am Soc Artif Intern Organs 1987; 33: 286-8.
21. Daugirdas JT. Rapid methods of estimating Kt/V: Three formulas compared. ASAIO Trans 1990; 36: M362-4.
22. Garred LJ, Canaud BC, McCready WG. Optimal hemodialysis: The role of quantification. Semin Dial 1994; 1: 236-45.
23. Schneditz D, Polaschegg HD, Levin NW, et al. Caridopulmonary recirculation in dialysis. An underrecognized phenomenon. ASAIO J 1992; 38: M194-6.
24. Sargent JA. Shortfalls in the delivery of dialysis. Am J Kidney Dis 1990; 15: 500-10.
25. Depner TA. Assessing adquacy of hemodialysis: Urea modeling. Kidney Int 1994; 45: 1522-35.
26. Peticlerc T, Man NK, Goureau Y, Jepenne G, Funck-Brentano JL. Optimization of sodium dialysate concentration by plasma water conductivity monitoring. In: Nosé Y, Kjellestrand C, Ivanovich P, eds. Progress in artificial organs. New York: Isao Press; 1985.
27. Locatelli F, Di Filippo S, Manzoni C. Monitoring sodium removal and delivered dialysis by conductivity. Int J Artif Organs 1995; 18: 716-21.
28. Santoro A. On-line monitoring (Editorial). Nephrol Dial Transplant 1995; 10: 615-8.
29. Keshaviah P, Ebben J, Luhving D, Emmerson P. Clincal evaluation of new on-line monitor of dialysis adequacy. J Am Soc Nephrol 1992; 3: 374.
30. Thomaseth K. PANSYM: A symbolic equation generation for

mathematical modeling, analysis and control of metabolic and pharmacokinetic systems. Comput Methods Programs Biomed 1994; 42: 99-112.

31. Thavarungkul P, Hakanson H, Holst O, Mattiasson B. Continuous monitoring of urea in blood during dialysis. Biosens Bioelectron 1991; 6: 101-7.
32. Lindsay R, Heidenheim P, Abunadar P, McCarthy G. On-line urea kinetic modeling: Preliminary results. Nephrol Dial Transplant 1993; 8: 995-6.
33. Depner T, Collins A, Jindal K, et al. Multicenter clinical validation of an on-line urea monitor (Abstract). J Am Soc Nephrol 1993; 4: 343-7.
34. Garred LJ, St Amour NR, McCready WG, Canaud BC. Urea kinetic modelling with a prototype urea sensor in the spent dialysate stream. ASAIO J 1993; 39: M337-41.
35. Stiller S, Wirt UD, Waterbar F, Gladziwa U, Dashnamurty KV, Mann H. Less symptomatic hypotension using BV-controlled ultrafiltration. Trans Am Soc Artif Intern Organs 1991; 37: 139-41.
36. Ronco C, Bellomo R. Central circulation, peripheral circulation and recirculation. Blood Purif 1997; 15: 334-45.
37. Linnenweber S, Lonnemann G. Pyrogen retention by the Asahi APS-650 polysulfone dialyzer during *in vitro* dialysis with whole human donor blood. ASAIO J 2000; 46: 444-7.