Nephrol Dial Transplant (2011) 26: 636–640
doi: 10.1093/ndt/gfq510
Advance Access publication 8 September 2010

The ultrafiltration coefficient of a dialyser (KUF) is not a fixed value, and it follows a parabolic function: the new concept of KUF max*

Alain Ficheux[1], Peter G. Kerr[2], Philippe Brunet[3] and Àngel Argilés[1,4]

[1]RD—Néphrologie, 104, rue de la Galéra, Ecole Nationale Supérieure de Chimie, 34090 Montpellier, France, [2]Department of Nephrology, Monash Medical Centre, Monash University, Melbourne, VIC, Australia, [3]Service de Néphrologie, Hôpital de La Conception—Université Aix-Marseille, 13005 Marseille, France and [4]Centre de dialyse de Sète, Néphrologie Dialyse St Guilhem, 34204 Sète, France

Correspondence and offprint requests to: Àngel Argilés; E-mail: argiles@rd-n.org
*The rights on the concept and data contained in this report have been protected by the patent numbers #08 56758 and WO/2010/040927.

Abstract

Background. Hydraulic permeability (KUF) is an intrinsic characteristic of dialysers, reported by the manufacturer as a single value, which drives and limits fluid removal. High-flux dialysers have been introduced with the appearance of convective techniques, aiming to increase fluid and solute removal. High convective volumes are being employed, although their advantages have not been fully demonstrated.
Methods. We assessed KUF over a pre-selected range of ultrafiltration rates (QUF) in post-dilutional haemodiafiltration and high-flux haemodialysis.
Results. KUF vs QUF was neither a fixed value nor a linear function but followed a parabolic function with a vertex der (y) = 0, which we have called KUF max. This also held true in high-flux routine dialysis.
Conclusions. These findings are completely new and have clear applications in clinics. The vertex point might be used to define the optimal QUF of a dialysis system, which would be that obtained at KUF max and corresponds to the best QUF/transmembrane pressure ratio, as opposed to the maximum QUF (which corresponds to the highest possible QUF), frequently associated with haemoconcentration, clotting, loss in dialyser surface area, and treatment problems. Determining KUF max *in vivo* could be of help in dialysis prescription and control with automatic systems.

Keywords: membrane permeability; physics of dialysis; ultrafiltration coefficient

Introduction

An improved knowledge of the physics of dialysis and progress in technology have allowed us to offer a safer and more comfortable treatment to an exponentially increasing worldwide dialysis population [1], since the first report on chronic dialysis treatment in 1960 [2].

Transmembrane pressure (TMP) and the membrane hydraulic permeability or ultrafiltration coefficient (KUF) regulate the rate and amount of fluid flow across the dialyser membrane.

Ultrafiltration flow greatly varies from the *in vitro* to the *in vivo* setting as it is influenced by blood components, such as haematocrit and total protein level. This has led to the development of a standardized measurement of ultrafiltration rate and KUF for dialysers, which is most commonly reported as millilitre per hour per millimetre of mercury ($mL \cdot h^{-1} \cdot mmHg^{-1}$) in an *in vitro* setting of animal blood, frequently bovine, controlled to include >60 g/L of total proteins and 32 ± 2% haematocrit (European norm: EN1283). KUF is widely believed to be a constant, and consequently, its value is reported by the manufacturer as a single value.

Hydraulic permeability, protein concentration and haematocrit greatly influence ultrafiltration rate [3–5], the main parameter in convective techniques, first described by Henderson *et al.* [6] and further developed with haemofiltration [7] and haemodiafiltration [8]. Ultrafiltration flow (QUF) increases linearly over a wide range of TMP (normally 200–500 mmHg), reaching a plateau where ultrafiltration flow does not vary following a TMP increase.

KUF is of outmost importance in high-flux convective techniques as it is the limiting factor for ultrafiltration flow and volume, and new dialysers with very high KUF values have been developed. At the same time, automatic systems to improve and to secure the convective techniques are sought by clinical investigators and practitioners as well as dialysis manufacturers.

In dialysis practice, to evaluate and control the performances in convection, using the dialysis monitors, the KUF of a dialysis system may be obtained by the following formula [9,10]:

$$\mathrm{KUF} = \mathrm{QUF}/\mathrm{TMP} \quad (1)$$

This formula measures what is happening across the entire dialysis membrane at a given time. It does not measure what is happening across a particular point in the membrane at a given time. To assess the latter, knowing oncotic pressure and its variations is necessary. Oncotic pressure is not measured by the dialysis monitors at the present time, and therefore, only the performances of the whole dialysis system may be reliably assessed in clinics.

We undertook a study aiming to establish an automatic system allowing control of the convective techniques and measured KUF *in vivo* during an online haemodiafiltration in clinics. We analysed KUF variation over pre-selected ranges of TMP and QUF.

Material and methods

TMP was derived from three-point measurements {mean pressure at the blood compartment [(inlet + outlet)/2] minus pressure at the dialysate compartment (measured at the dialysate outlet)}. Adding a third point of pressure measurement at the entrance of the blood compartment of the dialyser greatly improves the accuracy of the measures as it allows taking into account the loss of pressure experienced in the blood side. This prevents from the negative TMP readings that might be obtained with two-point measures. The addition of a fourth point of pressure measurement in the inlet of the dialysate compartment would complete the measurements. However, it requires modifications in the fluid circuit that are not presently ready for the clinical setting, and its impact on the readings is not as important (~7% of the maximal values of real TMP values); for these reasons, we used the three-point pressure measurements. QUF was the total ultrafiltration (infusion flow + weight loss/time), and KUF was calculated from (1).

Values of the different variables are given as mean ± standard deviation of the mean.

Eleven patients were treated three times a week in the dialysis centre of Néphrologie Dialyse St Guilhem with fully equipped AK200S machines (Gambro, Lund, Sweden) using ultrapure bi-reverse osmosis water. They had been on dialysis for more than 3 months and had no active disease at the moment of the analyses.

Haemodialysis and haemodiafiltration sessions were performed as normally conducted in the unit, and no interventional treatment was undertaken or evaluated. The information analysed in these studies exclusively consisted of retrieved values from the dialysis monitor while performing routine dialysis treatments using their usual dialysers. The patients gave their informed consent, and the study was performed in accordance with the Declaration of Helsinki.

Post-dilutional online HDF

Polyflux 210H (Gambro, Lund, Sweden, POLYAMIX™ membrane, 2.1 m² surface area and 85 $mL \cdot h^{-1} \cdot mmHg^{-1}$ *in vitro* KUF) were used by four patients. Ultrafiltration was increased manually by 10-mL/min steps of 30 seconds each. TMP and KUF were obtained. Six series of measurements were performed per patient. Total dialysate production was 600 mL/min, blood flow was 339 ± 30 mL/min (range 308–370 mL/min) and mean weight loss was 0.6 ± 0.2 L/h (range 0.4–0.9 L/h). Infusion flow was increased stepwise, from 0 to a maximum of 30% of the blood flow.

Haemodialysis

XEVONTA HI 2.3 (B.BRAUN–AVITUM, Melsungen, Germany, polysulphone membrane, 2.3 m² surface area, *in vitro* KUF is 124 $mL \cdot h^{-1} \cdot mmHg^{-1}$) filters were used by seven patients. One series of measurements was performed per patient. Total dialysate production was 500 mL/min, and blood flow was 347 ± 22 mL/min (range 340–390 mL/min). Ultrafiltration flow was increased stepwise, in the same manner as for online haemodiafiltration.

Milk experiments

Ultrafiltration was also checked in an *in vitro* system containing milk as a protein-containing cell-free fluid. Two XEVONTA HI 2.3 filters were used. Four series of measurements were performed per filter. Milk flow was 320 ± 10 mL/min.

Results

The results of the KUF obtained with increasing values of QUF are presented in Figure 1. Firstly, to our surprise, KUF vs QUF was not a single value nor a linear function, but it exhibited a parabolic shape following a function with upper convexity, whose maximum value is the vertex of the parabolic function [der (y) = 0]. Secondly, KUF traditionally provided by the manufacturers as a single value varied from <20 to >45 $mL \cdot h^{-1} \cdot mmHg^{-1}$, a range of greater than ×2.5-fold. Thirdly, the shape was very reproducible for a given patient with a given dialysis setting, and it never plateaued.

The variability of KUF contrasted with the variability of the value of QUF at which the vertex of KUF was obtained, which was remarkably low (it varied between 55 and 59 mL/min with a SD of 1 mL/min, represented in the figure by the bar on the vertical line; 57.4 ± 1.1 mL/min, variation coefficient = 1.9%). Finally, the vertex value of KUF obtained in five measurements was also remarkably constant, varying from ~44 to ~47 $mL \cdot h^{-1} \cdot mmHg^{-1}$ ($45.8 \pm 1.2\ mL \cdot h^{-1} \cdot mmHg^{-1}$, variation coefficient = 2.6%).

To check the reproducibility of these findings, four patients treated with the same dialyser type were assessed. Six series of measurements were performed per patient. KUF followed the parabolic function on differential increases in QUF with an increasing phase, a vertex and a decreasing phase. As illustrated in Figure 2, the vertices of the parabolas were observed to be in a narrow range of both KUF (y-axis) and QUF (x-axis), demonstrating that the KUF max was quite constant for a given dialysis setting and that the QUF obtained with the best QUF/TMP ratio varied little within in a narrow range. KUF max of the 24 measurements was 52 ± 12 $mL \cdot h^{-1} \cdot mmHg^{-1}$, and the QUF at which KUF max was obtained was 65 ± 8 mL/min. Six curves clearly reached a higher KUF max; these were all from the same patient. Therefore, the measurements were very reproducible for a given patient, but varied from patient to patient, even when using the same dialysis setting (identical dialyser and dialysis system).

KUF was also measured in haemodialysis mode using high-flux dialysers. It varied following the same patterns observed in haemodiafiltration: an ascending phase, a vertex and a descending phase with an increase in QUF (Figure 3). This variation was observed in all the seven patients included in the study.

As an extension of the present study, we also assessed the KUF variation over QUF in an *in vitro* system using a fluid containing proteins and free of cells. We used milk instead of blood. The results confirmed those obtained *in vivo* with blood: the KUF over QUF variations followed the same parabolic function (Figure 4).

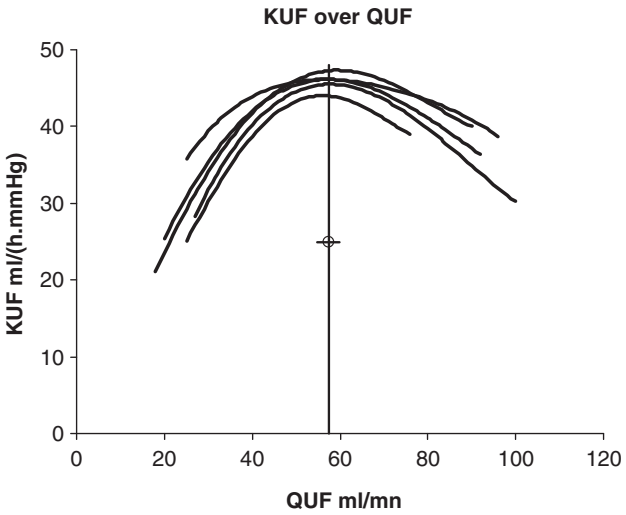

Fig. 1. KUF vs QUF in haemodiafiltration. Five independent measurements were performed. It was observed that KUF values displayed a parabolic curve following QUF increases, with an increasing phase, a vertex and a decreasing phase for the higher values of QUF. The variability of KUF was strikingly high (range of ×2.5-fold). This contrasted with the variability of the value of QUF at which the vertex of KUF was obtained, which was remarkably low.

Discussion

In the present study, we identified that KUF is not a single value inherent to the membrane in a real clinical setting, and it follows a parabolic function when plotted against QUF. The curve has a first part with KUF increasing linearly (in the low QUF range), a vertex, which represents the KUF max, and a descending part. Several historical points could have alerted us to the flaw of considering KUF as a constant. It is well established that KUF is influenced by haematocrit and protein concentration [4,5], which vary during dialysis, and Eloot *et al.* have characterized the KUF reduction due to the protein layer formation in the filter [11]. Pallone *et al.* [12] in a well-controlled *in vitro* system observed variations in the KUF that they characterized at the membrane level. Furthermore, the distribution of internal filtering surfaces of the dialyser [net filtering surface and the surface with a reversed fluid flow (back-filtration)] may change under some circumstances [13,14], forcedly resulting in a variation of the KUF. A shift in the internal point of the dialyser where back-filtration appears, relatively decreasing the back-filtration surface which would even disappear in the high QUF rates, could explain at least in part the increase in KUF observed in the present study.

Discordances between the obtained weight loss and that targeted according to the KUF given by the manufacturer were rather uncommon with low-flux dialysers. With the introduction of high-flux dialysers, built-in ultrafiltration control [15] became mandatory, as TMP monitoring was not sufficient to guarantee an accurate volume control [16]. High-flux membranes have larger pores allowing greater rates of passage across the membrane of water and solute, improving middle-molecular-weight uraemic retention solute removal [17–21]. However, increasing convective volumes as much as possible (QUF max) in haemodiafiltration and haemofiltration is only obtained with very high TMPs, increasing viscosity, and inducing a protein layer formation and sometimes clotting of fibres of the dialyser with effective surface reduction.

Indeed, Henderson *et al.* [9] demonstrated that the sieving coefficient for plasma solutes decreases with an increase in ultrafiltration flow. As a consequence, in the system used by Henderson and colleagues (with Amicon D30 membranes), solute removal was enhanced

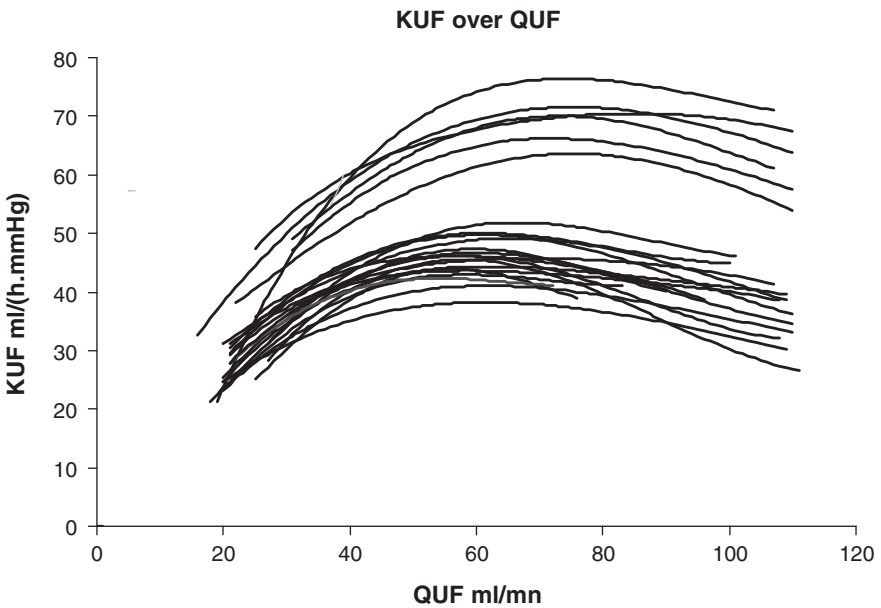

Fig. 2. Reproducibility of KUF max in post-dilutional online haemodiafiltration. Four patients treated with the same dialyser are represented. Six series of measurements were performed per patient. KUF followed the parabolic function on differential increases in QUF with an increasing phase, a vertex and a decreasing phase. The six curves clearly reaching a higher KUF max were from the same patient.

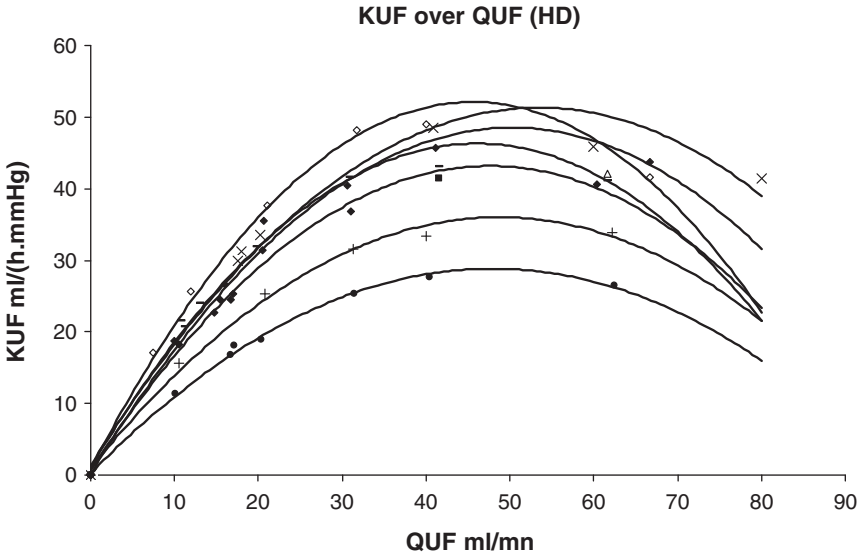

Fig. 3. KUF during high-flux haemodialysis. Serial increases of QUF were applied in *in vivo* haemodialysis using high-flux dialysers. KUF also followed a parabolic function on differential increases in QUF with an increasing phase, a vertex and a decreasing phase.

with a decrease in QUF. The application of our findings reported here should allow the objective definition of the best possible conditions to improve the rheology of the system. The dialysis monitor could be equipped with an automatic system to determine KUF and particularly KUF max by increasing QUF over a short period of time. Then, the infusion flow for haemodiafiltration could be regulated in a precise manner to maintain the system at the KUF max.

If we think about proposing KUF max to monitor haemodialysis and haemodiafiltration systems, the variability on its determination is a crucial point to consider. As it is shown in Figure 1 and also in Figure 2, repeating the measurements while the dialysis session progresses showed a relatively low variability in the absolute value of KUF max. Although it slightly decreased with time, the variation coefficient for a single patient was only 2.6%. The variability is even smaller if we look at the QUF at which KUF max is obtained, with a variation coefficient <2%.

These low variation coefficients render KUF max and QUF at which KUF max is obtained, interesting parameters that might be suitable to monitor the performances

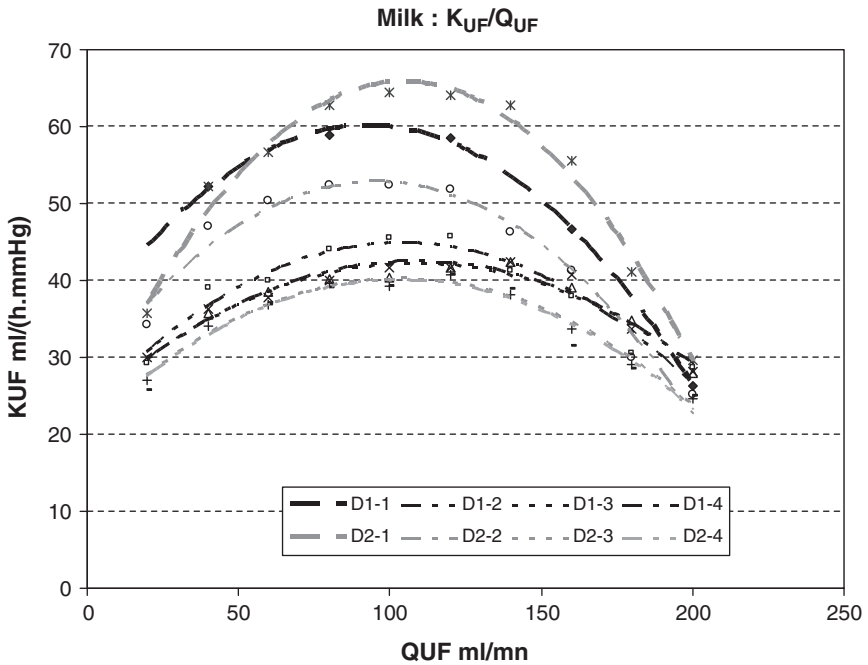

Fig. 4. KUF during high-flux ultrafiltration of an *in vitro* system using milk. QUF was increased in an *in vitro* ultrafiltration system using two different high-flux dialysers. KUF followed the same pattern than that observed in our *in vivo* haemodialysis and haemodiafiltration studies.

of a dialysis or haemodiafiltration system. However, the real benefits that their use may provide await confirmation by clinical studies.

Our milk experiments show that the present findings are also potentially relevant for other non-medical systems using ultrafiltration-based techniques, such as the preparation of drinking water for the community as well as dairy and fruit juice industries [22,23].

In summary, our findings show that KUF in haemodialysis and haemodiafiltration is a variable parameter, and a single manufacturer's value cannot be relied upon. Furthermore, we have demonstrated that KUF varied by increasing QUF in a parabolic way with a maximum value (the vertex of the parabola) which corresponded to the best QUF/TMP ratio. This introduces the new concept of KUF max, which should be more appropriately used as a characteristic of a dialyser, and allows defining what would be the optimal QUF of a dialysis system.

Using a QUF max approach in post-dilutional haemodiafiltration frequently results in an increased number of alarms and 'by pass' time, as well as the required nurse interventions, likely due to protein cake formation and excessive haemoconcentration and hypercoagulability, and pre-dilutional, mid-dilution and mixed haemodiafiltration have been proposed to overcome these problems [24,25]. Maintaining the system at KUF max, although it decreases the total convection volume, is likely to reduce these technique-linked inconveniences.

Acknowledgements. This work has been possible with the collaboration of the nursing staff of NDSG particularly Marie Thomas. The help of Gilles Goubert has been very much appreciated.

Conflict of interest statement. A.F. and A.A. have declared to be employees of the SAS—RD Néphrologie, owner of the patent numbers #08 56758 and WO/2010/040927 protecting the exploitation rights of the concept of KUF max, of which they are the inventors. P.G.K. and P.B. have declared no competing financial interests.

(See related article by Schneditz. TMP revisited: the importance of plasma colloid osmotic pressure in high-flux dialysers. *Nephrol Dial Transplant* 2011; 26: 411–413.)

References

1. United States Renal Data System (USRDS) Report for 2008 (http://www.usrds.org) (4 July 2010, date last accessed).
2. Scribner BH, Buri R, Caner JEZ *et al*. The treatment of chronic uremia by means of intermittent hemodialysis: a preliminary report. *ASAIO* 1960; 6: 114–122
3. Michaels AS. New separation technique for the CPI. *Chem Eng Prog* 1968; 64: 31–42
4. Blatt WF, Dravid A, Michaels AS *et al*. Solute polarization and cake formation in membrane ultrafiltration: causes, consequences and control techniques. In: JE Flinn (ed). *Membrane Science and Technology*. New York: Plenum Press, 1970; 47–95
5. Okazaki M, Yoshida F. Ultrafiltration of blood: effect of hematocrit on ultrafiltration rate. *Ann Biomed Eng* 1976; 4: 138–150
6. Henderson LW, Besarab A, Michaels A *et al*. Blood purification by ultrafiltration and fluid replacement (diafiltration). *Trans Am Soc Artif Intern Organs* 1967; 13: 216–226
7. Henderson LW, Colton CK, Ford CA. Kinetics of hemodiafiltration. II. Clinical characterization of a new blood cleansing modality. *J Lab Clin Med* 1975; 85: 372–391
8. Mann H. Influences of the site of diluting fluid substitution on hemodiafiltration processing. *J Dial* 1977; 1: 559–566
9. Henderson L. Biophysics of ultrafiltration and hemofiltration. In: Jacobs C, Kjellstrand C, Koch K, Winchester J (eds). *Replacement of Renal Function by Dialysis*. 4th edn. Dordrecht: Kluwer Academic Publishers, 1996; 114–145
10. Sargent JA, Gotch FA. Principles and biophysics of dialysis In: Drukker W, Parsons FM, Maher JF (eds). *Replacement of Renal Function by Dialysis*. The Hague; Boston; London: Martinus Nijhoff Publisher, 1978; 38–68
11. Eloot S, De Wachter D, Vienken J *et al*. In vitro evaluation of the hydraulic permeability of polysulfone dialysers. *Int J Artif Organs* 2002; 25: 210–216
12. Pallone TL, Petersen J. Continuous arteriovenous hemofiltration: an in vitro simulation and mathematical model. *Kidney Int* 1988; 33: 685–698
13. Clark WR, Rocha E, Ronco C. Solute removal by hollow-fiber dialyzers. *Contrib Nephrol* 2007; 158: 20–33
14. Ronco C, Brendolan A, Feriani M *et al*. A new scintigraphic method to characterize ultrafiltration in hollow fiber dialyzers. *Kidney Int* 1992; 41: 1383–1393
15. Kozlov JG, Khaitlin AE, Lisitsina K. *Device for preparation of a dialysing solution*. US patent 3804107, 16 April 1974
16. Polaschegg HD, Levin NW. Hemodialysis machines and monitors. In: Jacobs C, Kjellstrand CM, Koch KM (eds). *Replacement of Renal Function by Dialysis*. 4th edn. Dordrecht, the Netherlands: Kluwer Academic Publishers, 1996; 333–379
17. Kerr PG, Argiles A, Flavier JL *et al*. Comparison of hemodialysis and hemodiafiltration: a long-term longitudinal study. *Kidney Int* 1992; 41: 1035–1040
18. Eknoyan G, Beck GJ, Cheung AK *et al*. For the Hemodialysis (HEMO) Study Group. Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 2002; 347: 2010–2019
19. Hakim RM, Held PJ, Stannard DC *et al*. Effect of the dialysis membrane on mortality of chronic hemodialysis patients. *Kidney Int* 1996; 50: 566–570
20. Koda Y, Nishi S, Miyazaki S *et al*. Switch from conventional to high-flux membrane reduces the risk of carpal tunnel syndrome and mortality of hemodialysis patients. *Kidney Int* 1997; 52: 1096–1101
21. Leypoldt JK, Cheung AK, Carroll EC *et al*. Effect of dialysis membranes and middle molecule removal on chronic hemodialysis patients survival. *Am J Kidney Dis* 1999; 33: 349–355
22. Wu D, Howell JA, Field RW. Critical flux measurement for model colloids. *J Membr Sci* 1999; 152: 89–98
23. Espinasse B, Bacchin P, Aimar P. On an experimental method to measure critical flux in ultrafiltration. *Desalination* 2002; 146: 91–96
24. Krieter DH, Collins G, Summerton J *et al*. Mid-dilution on-line haemodiafiltration in a standard dialyser configuration. *Nephrol Dial Transplant* 2005; 20: 155–160
25. Pedrini LA, De Cristofaro V, Pagliari B *et al*. Mixed predilution and postdilution online hemodiafiltration compared with the traditional infusion modes. *Kidney Int* 2000; 58: 2155–2165

Received for publication: 30.11.09; Accepted in revised form: 27.7.10