In vitro and in vivo evaluation of a new dialyzer

Michael Küll1, Bernd Nederlof1 and Hans Schneider2

1Fresenius Medical Care, Bad Homburg, Germany and 2Nephrology Center Stuttgart, Stuttgart, Germany

Abstract

Background. Recent dialyzer-related developments have concentrated upon the improvement of performance and biocompatibility. The focus of these developments was predominantly on the membrane itself. A newly developed high-flux dialyzer (FX60) with an advanced Fresenius Polysulfone® membrane (Helixone®) overcomes this limitation and has several design-related advantages attributed to the redesign of the individual functional components. For the first time, polypropylene was selected as the material for the dialyzer housing. Both the fibre and the fibre-bundle geometry were refined with the aim of improving overall performance and to reduce dialysate consumption.

Methods. This study aims at investigating the in vitro and in vivo performance of the new FX60 dialyzer with the focus on dialysate flow distribution and dialysate consumption. A new method to analyse dialysate flow distribution, based on local clearances, is suggested. The effect of reducing dialysate flow from 500 to 300 ml/min is investigated in vivo.

Results. $K_{bA_\text{urea}}$, a common measure to quantify device performance, is found to approach 1000 ml/min for the FX60 with a surface of only 1.4 m². Local clearance measurement shows equal performance of the Helixone® fibre bundle over the entire cross-section. A dialysate flow reduction by 20% (in vivo) only results in a minor loss in clearance.

Conclusions. The newly developed high-flux dialyzer (FX60) shows a remarkable performance ($K_{bA_\text{urea}}$). The excellent utilization of dialysate could be proven in vivo and is attributed to the superior dialysate flow distribution. A reduction of dialysate flow by 20% could lead to substantial economic savings.

Keywords: dialysate consumption; dialysate flow distribution; high-flux dialyzer; local clearance; polysulfone membrane

Introduction

Major changes in dialyzer design have taken place over the past 30 years [1–3]. Coil dialyzers, which were widespread in the early 1970s, are no longer in use and parallel plate dialyzers are rarely applied today. Nowadays, the standard dialyzer is a capillary dialyzer as already introduced in the mid 1960s by Dow Cordis. The design and handling of the capillary dialyzers has remained almost unchanged since then. However, various membranes have been developed in an attempt to improve biocompatibility or performance. As the focus of these developments was predominantly on the membrane itself, the module has never undergone a complete redesign and, thus, should offer considerable improvement potential.

A recent development has overcome this limitation. The FX dialyzer series includes an advanced Fresenius Polysulfone® membrane, called Helixone® [4,5] and compared with conventional dialyzers, almost all components of the FX class of dialyzers have undergone significant modifications to improve the overall device performance.

A very light, environmentally friendly material—polypropylene—was chosen to manufacture the FX-class dialyzer housing. For a given effective surface area, the housing diameter was reduced without altering the length; this improves the dialysate flow distribution because of a higher average flow velocity.

In the conventional dialyzer design, dialysate enters straight through the dialysate port (and only from one side) into the actual fibre compartment. This often leads to an inappropriate dialysate distribution, with the dialysate flowing directly from the inlet to the outlet leading to poor coverage of large parts of the fibre bundle. In this new design, the special pinnacle structure of the housing acts as a dialysate distributor and ensures that dialysate enters from all sides into the fibre bundle at similar flow rates. This contributes to a more homogeneous dialysate flow distribution.

It is well known that dialysate flow distribution in standard dialyzers is sub-optimal, especially when fibre bundles with a larger diameter are used. Usage of spacer yarns in different variations is one approach
used for the optimization of dialysate flow distribution. In the FX class a different approach has been taken: a special ondulation, the micro-crimp geometry, of the fibres ensures that high-fibre bundle-packing densities can be realized whilst still being sure that single fibres do not come too close to one another. This allows an increase of fibre-packing density from 45 to 60% of the theoretical maximum.

While in a standard dialyzer, the pressure drop on the dialysate side is almost negligible, a denser fibre bundle increases the pressure drop, thereby enhancing internal filtration and leading to an improved middle-molecular clearance during a standard haemodialysis treatment [6].

In addition to the fibre bundle as a whole, the geometry of a single fibre yields improvement potential. Unlike cellulosic membranes, synthetic dialysis membranes have a larger wall thickness, which results in a larger diffusive resistance, leading to a reduction in the diffusive clearance especially for the smaller molecules. The reduction of wall thickness by more than 10% down to 35 µm (from 40 µm) improves small molecular clearance without any loss of mechanical stability.

Internal filtration is dependent on fibre bundle and the single-fibre geometry. By reducing the fibre diameter from 200 to 185 µm, the pressure drop increases by approximately 25%, resulting in a higher internal filtration and an improved middle-molecular clearance [7].

It is the aim of this paper to demonstrate that the new dialyzer design described above was successful in improving overall dialyzer performance. Clearances are reported in vitro and in vivo. A new clearance-based method to analyse dialysate flow distribution is suggested and applied. The influence of a dialysate flow reduction on clearances was investigated in vivo.

**Subjects and methods**

In this study, the new Fresenius FX60 dialyzer (surface 1.4 m², membrane lumen 185 µm, number of fibres approximately 10 000) with the advanced high-flux membrane Helixone® (Fresenius Medical Care, Bad Homburg, Germany) was investigated using the following methodologies.

**Clearance evaluation**

In vitro clearance data were determined according to the European Norm (EN 1283) as follows. The blood flow, \( Q_B \), was varied within the recommended blood flow range. The dialysate flow, \( Q_D \), was set to 500 ml/min, and the net ultrafiltration, \( Q_f \), was carefully adjusted to zero. The temperature was stabilized at 37°C. The dialysate and the aqueous test solution used on the blood side were used in single-pass mode and not re-circulated.

Samples of the test solution were taken from the inlet and the outlet of the dialyzer and the concentration of the different analytes was determined. The clearance was calculated according to the following formula:

\[
K = \frac{Q_B \times (C_{B0} - C_{B})}{C_{B0}}
\]

where \( K \) is the clearance, \( Q_B \) is the blood flow, \( C_{B0} \) is the solute concentration at the dialyzer inlet, and \( C_B \) is the solute concentration at the dialyzer outlet.

**K₀A calculation**

To specify dialyzer performance for a given solute it is necessary to give a clearance for each blood flow. The parameter \( K_0A \) (mass transfer area coefficient) [8], which is finding increasing usage in particular in the USA, overcomes this difficulty. To a very good approximation, a single \( K_0A \) value is sufficient to describe dialyzer performance for a given solute. For any given \( K_0A \), clearances under varying blood and dialysate flow conditions can be calculated according to the following formula:

\[
K = \frac{\exp\left(\frac{K_0A \times (1 - Q_u/Q_B)}{Q_u}\right) - 1}{\exp\left(\frac{K_0A \times (1 - Q_u/Q_B)}{Q_u}\right)} - 1
\]

where \( K_0A \) is the mass transfer area coefficient specified by the manufacturer, \( K \) is the clearance, \( Q_B \) is the blood flow, and \( Q_D \) is the dialysate flow (all parameters in millilitre per minute).

**Measurement of local clearances**

Different methods for determining dialysate flow distributions are available, reaching from complex approaches like nuclear magnetic resonance measurements to very simple methods like dye injection. Our approach was different. If certain areas in a dialyzer are not sufficiently perfused with dialysate, the clearance in these areas is poor. Therefore, the most direct way to identify flow distribution non-uniformity is to check local clearances. To do so, a standard experiment for the in vitro determination of clearances was set up. Both dialysate and ‘blood’ reservoir were used, single-pass and net ultrafiltration was adjusted to zero. The only modification was the use of a different end cap on the blood outlet side. This end cap is divided into 25 areas with a separate net ultrafiltration was adjusted to zero. The only modification was the use of a different end cap on the blood outlet side. This end cap is divided into 25 areas with a separate outflow thus allowing the collection of samples from different areas separately. The flow in each segment is determined individually as well as the local clearance calculated according to:

\[
K_L = Q_{B,L} \times \frac{C_{B,L} - C_{B0,L}}{C_{B0}}
\]

where \( K_L \) is the local clearance, \( Q_{B,L} \) is the local blood flow, \( C_{B,L} \) is the solute concentration at the dialyzer inlet, \( C_{B0,L} \) is the local solute concentration at the dialyzer outlet, and \( L \) is an index labelling different cross-sectional areas.

**In vivo clearance data—dependency on dialysate flow**

A group of 10 stable outpatients undergoing chronic haemodialysis treatment for an average of 57.5 months, mainly using high-flux dialyzers (F60 S), was switched to the new FX60 capillary dialyzers and was monitored for more than 6 months. Clinical visits and standard laboratory results were documented at the beginning and after 6 months, and were then compared. Treatment modalities were kept stable as far as the clinical situation permitted. Dialysate flow
rates were 400 ml/min, blood flow rates increased from 315 ± 30 ml/min at the beginning to 365 ± 47 ml/min more than 6 months later. Treatment times were kept constant with 13.65 ± 1.31 h/week on a three-dialysis session per week basis. Furthermore, clearance values of urea, creatinine, uric acid, phosphate, and β₂-m were obtained using blood flow rates of 300 ml/min and dialysate flow rates of 500, 400, and 300 ml/min for a period of 2 weeks, respectively. Plasma samples were obtained at the inflow and outflow sites of the FX60 dialyzer 60 min after starting the midweek dialysis. Filtrate rates were reduced to zero, 2 min prior to sampling in order to avoid additional convection. Unchanged amounts of heparin were given continuously during the dialysis sessions.

**Results**

**Clearance and $K_0A$ determination**

Figure 1 shows *in vitro* clearance data for urea and inulin for the FX60 in the recommended blood flow range. The dialysate flow, $Q_D$, was set to 500 ml/min and the net ultrafiltration was zero. Data from three sample determinations are shown. Also shown are calculated clearance values using $K_0A = 967$ ml/min for urea and $K_0A = 144$ ml/min for inulin being in excellent accordance with the measured values. As the orders of magnitude for $K_0A$ may not be as familiar to everybody as clearances are, the respective numbers for the F60 S are given: $K_0A_{urea} = 727$ ml/min and $K_0A_{inulin} = 131$ ml/min. The $K_0A$ values for urea and inulin, as specified above, were not calculated from a single clearance measurement at a fixed blood and dialysate flow rate. Instead, a least square fit algorithm was used to find the best approximation of the aforementioned clearance formula to a variety of measured clearances under different flow conditions (all data not shown here).

It might be surprising that the $K_0A$ concept, founded theoretically on pure diffusion principles, reproduces laboratory data in such an excellent way, even though a significant amount of internal filtration is present in FX-class dialyzers. The *in vitro* internal filtration of the FX60 is estimated to be approximately twice as high as compared with the F60 S.

**Measurement of local clearances**

To check the dialysate flow distribution, clearances were determined for individual cross-sectional areas of the FX60 and compared with a standard dialyzer. The results obtained for a standard fibre bundle and the new Helixone® fibre bundle are shown in Figure 2. In a standard bundle design, clearance is better in the outer areas and drops by approximately 20% towards the centre. In contrast, the Helixone® fibre bundle leads almost to constant clearance distribution over the whole cross-section.

**In vivo clearance data—dependency on dialysate flow**

Urea clearance values with 300 ml/min blood flow and 500 ml/min dialysate flow rates were found to be $242 ± 19$ ml/min and reduced to $221 ± 28$ ml/min (−8.5%) at a 400 ml/min dialysate flow. As expected, a further reduction to $211 ± 34$ ml/min (−12.6%) was demonstrated at a 300 ml/min dialysate flow. Creatinine clearance values were determined: $172 ± 17$ ml/min at a dialysate flow of 500 ml/min, with a reduction to $168 ± 17$ (−1.9%) and $164 ± 25$ ml/min at 400 and 300 ml/min dialysate flow. For phosphate, we found a plasma clearance of $182 ± 28$ ml/min at 500 ml/min, $180 ± 29$ ml/min (−1.1%) at 400 ml/min, and $175 ± 27$ ml/min at 300 ml/min dialysate flow rate. Uric acid clearances were $191 ± 19$ ml/min at 500 ml/min, $190 ± 15$ ml/min (−0.5%) at 400 ml/min,
and 184 ± 25 ml/min at 300 ml/min dialysate flow. β2-m clearance values measured 78 ± 12 ml/min at 500 ml/min, 78 ± 16 ml/min (0%) at 400 ml/min, and 69 ± 13 (−10.5%) at 300 ml/min dialysate flow (see Figure 2).

**Discussion**

The new FX60 dialyzer was designed to achieve optimal performance under various treatment conditions. The well-known standard housing design has been re-engineered to achieve this goal. Membrane permeability and geometry as well as fibre-bundle design were also adapted. One of the main targets was to improve performance.

This study investigated *in vitro* and *in vivo* performance of the FX60 dialyzer with a special focus on dialysate flow distribution. The *in vitro* and *in vivo* data given show that the design efforts resulted in excellent clearance values approaching a $K_aA$ value for urea of 1000 ml/min (30% above F60 S performance) with only 1.4 m² of membrane surface. Optimization of dialysate flow distribution lead to almost constant local clearances over the entire cross-section of the dialyzer.

The excellent utilization of dialysate could be proven *in vivo* as well. Clearances for different marker
molecules were determined in vivo at dialysate flow rates of 300, 400, and 500 ml/min. Theoretically, the decrement of clearances with reduction of dialysate flow rates is most impressive regarding small molecular weight substances and subsequently diminishes with increasing molecular weight shedding information about the importance of convective transport properties for the elimination of high molecular weight substances. The in vivo clearance properties of the FX60 dialyzer shown in Figure 3 are very close to the data, which have been expected by computer simulation.

If dialysate flow rates are lowered from 500 to 400 ml/min (a 20% reduction), for clearance values of small molecular weight substances a decrease of only between 1 and 9% occurs. This small decrement was achieved by the new fibre-bundle design leading to an optimized dialysate flow distribution. In view of the fact that in most dialysis facilities in Europe, blood flow rates are well below maximal values (with respect to fistula performance and surface of the dialyzer used), it may be recommended to increase blood flow rates by 10%. This increase would easily abolish the loss of clearance performance through a dialysate flow reduction of 20% bringing with it substantial economic savings.

References

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