PERFORMANCE CHARACTERISTICS OF HIGH FLUX
HAEMODIAFILTRATION

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Summary

With the described technique of high diffusive and convective solute transport an almost threefold increase in efficiency over conventional dialysis was clinically demonstrated. Coupled with the better tolerance to high solute and weight removal rates, this approach permits drastic reduction of treatment time, without sacrificing treatment adequacy.

Introduction

The goal of any renal replacement therapy for end-stage renal disease should be to maintain the patient's solutes within acceptable ranges, remove interdialytic weight gain and, for obvious socio-economic reasons, do both in the shortest possible time. It follows that treatment time must not be reduced unless it is accompanied by an at least commensurate increase in solute and weight removal rates. Efforts to augment efficiency in conventional acetate haemodialysis are effectively curtailed by clinical intolerance to high solute transfer and ultrafiltration rates [1,2]. The standard technique, as it has emerged over the years, mirrors these limitations and consists of comparatively low blood and dialysate flow rates as well as membranes with low hydraulic permeability and surface area. Previously thought to be absolute, this barrier to efficiency was challenged in recent years by observations of better treatment tolerance with bicarbonate dialysis, haemofiltration and haemodiafiltration [3–6]. The key elements of these techniques, a greater convective solute transport component and bicarbonate dialysate, were recently combined in a new modality termed high flux haemodiafiltration. By augmenting simultaneously blood and dialysate flow rates as well as membrane surface area and permeability a more than twofold increase in efficiency over conventional haemodialysis was achieved with this technique [7]. Clinical tolerance to high solute and weight removal rates permitted the reduction of treatment time to under six hours weekly, without sacrificing treatment adequacy [8].

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The present clinical study explores the gains in efficiency to be made by further augmenting blood flow rates and evaluates the performance of different membranes with greater permeability in high flux haemodiafiltration.

Materials and methods

The study was performed with four stable end-stage renal disease patients who had mature forearm Cimino-Brescia fistulae. Cannulation was by 14-gauge, 1 inch needles (LifePath®, Drake Willock). Haemodiafiltration was performed in a new mode, described in greater detail elsewhere [7]. Three different hollow fibre dialysers were evaluated, made of a new anisotropic polysulfone membrane (1.25m², Hemoflow F-60, Fresenius AG), polymethylmethacrylate (2.1m², Filtryzer B1L, Toray Industries) and an older model of cellulose acetate (1.8m², C-DAK DuoFlux, Cordis Dow). The listed dialysers were used in pairs in a serial configuration in the extracorporeal circuit. Sterile, pyrogen-free dialysate was delivered at 1000 ± 22ml/min in countercurrent mode by an automated system providing volumetric control of net ultrafiltration. By adjusting differential pressures, maximal ultrafiltration was obtained in the first device, while volume replacement by backfiltration of dialysate occurred in the second device. In this serial configuration the entire surface area of both devices was available for diffusion. Dialysate composition was Na 140, K 2, Ca 4.5, Mg0.7, Cl 108.2, HCO₃ 35, Acetate 4mEq/L and glucose 100mg/100ml.

During the clinical treatment the performance was routinely evaluated by whole blood clearances obtained from blood and dialysate [7]. Blood flows were measured by using occlusive blood pumps calibrated at the same input and output pressures as encountered clinically. Dialysate flow rates were measured by timing the strokes of the proportioning cylinders, whose volume had previously been calibrated. Net weight loss was determined from the slope of a continuous recording of the weight of the bed scale plus the patient. Ultrafiltration rate in the first device was measured by a ball-in-tube flow meter (FL1300, Gilmont Instruments) during brief periods when the dialysate flow to this dialyser had been bypassed, but pressures maintained at operating levels. Pressures were automatically measured using differential transducers (140 PC, Microswitch) and continuously recorded by a microcomputer (TRS 80©). Solute concentrations were determined by the Autoanalyser technique. The erythrocytes were allowed to equilibrate with plasma for at least one hour before separation. Inulin (American Critical Care) was injected in bolus of 2g intravenously at least 10 minutes before clearance periods. Plasma inulin was analysed by the Anthrone method for Autoanalyser, and clearances were calculated using plasma flows.

In order to exclude possible measurement errors, all clearance periods were analysed for mass balance error of urea [9]. Only periods with a urea mass balance error of less than 10 per cent were used for analysis. The reported whole blood clearances are means of values calculated from both blood and dialysate concentrations.
Results

All treatments, where the high flows and clearances were maintained throughout, were well tolerated by the patients. Treatment times were less than two hours, three times weekly.

Fluid movements across the membrane in the described serial configuration are illustrated in Figure 1. The upper panel depicts ultrafiltration from blood to dialysate occurring in the first device of the serial configuration in response to a range of positive or forward transmembrane pressure gradients. Back filtration from dialysate to blood, occurring simultaneously in the second device in response to automatically adjusted negative or reverse transmembrane pressure gradients, is shown in the lower panel. Note that it takes less negative or reverse transmembrane pressure to transfer back filtrate into blood than it takes to ultrafiltrate the same volume from the blood.

Compared to conventional haemodialysers, all of the evaluated membranes
demonstrated substantially greater hydraulic permeabilities. If surface area is taken into account, the new polysulfone membrane performed best followed by polymethylmethacrylate and cellulose acetate.

The overall performance for solute removal of the different devices in series is summarised in Table I. Listed are whole blood clearances for urea, creatinine, phosphorus and inulin in high flux haemodiafiltration (Q_B = blood flow, Q_D = dialysate flow, Q_F = ultrafiltration in the first device of the serial configuration).

<table>
<thead>
<tr>
<th>Q_B = 630 ± 14</th>
<th>Q_D</th>
<th>Q_F</th>
<th>Cl_BUN</th>
<th>Cl_Cr</th>
<th>Cl_P</th>
<th>Cl_In*</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-60 (2 x 1.25m²)</td>
<td>1006 ± 11</td>
<td>146 ± 18</td>
<td>514 ± 12</td>
<td>432 ± 7</td>
<td>399 ± 29</td>
<td>171</td>
</tr>
<tr>
<td>BIL (2 x 2.1m²)</td>
<td>1008 ± 13</td>
<td>127 ± 38</td>
<td>480 ± 7</td>
<td>377 ± 9</td>
<td>373 ± 16</td>
<td>163</td>
</tr>
<tr>
<td>DuoFlux (2 x 1.8m²)</td>
<td>992 ± 34</td>
<td>111 ± 39</td>
<td>446 ± 17</td>
<td>366 ± 24</td>
<td>357 ± 69</td>
<td>148</td>
</tr>
</tbody>
</table>

n=5 (ml/min, mean ± SD)
* = plasma clearance, n=2

phosphorus and plasma clearances for inulin obtained during clinical treatment at a blood flow rate of 630ml/min. Also listed are the measured rates of dialysate flow as well as ultrafiltration (Q_F) in the first device of the serial configuration.

Dependence of urea clearance on blood flow is illustrated in Figure 2, where the data from Table I are depicted in comparison to values obtained at a Q_B of 500ml/min. In terms of performance the evaluated membranes ranked in an identical order as seen for hydraulic permeability above.

Discussion

To our knowledge, clinically obtained solute clearances of this magnitude have not been reported previously. This almost threefold gain in efficiency over conventional dialysis was achieved by augmenting all the factors limiting performance in the extracorporeal circuit. The single most important under-utilised resource to increase efficiency is the blood flow delivering the solute to the membranes. Actual blood flows in mature vascular accesses substantially exceed the flow rates used in conventional dialysis and may be up to 2L/min in many patients [10]. Given an optimal technique, bypassing a larger fraction through the extracorporeal circuit in itself poses no additional risk for the patient.

In order to fully exploit higher blood flow rates, every other factor contributing to mass transfer must be optimised. To maintain solute gradients, dialysate flow must be proportionally increased. The doubling of surface area in our serial configuration maintains flow dependence of clearance even in the range illustrated in Figure 2. The effect of high surface area and simultaneous diffusion and convection on solute transport is apparent from the magnitude of the
clearances obtained for small as well as large solutes. The comparison between the different membranes in our study indicates that diffusive permeability correlates with hydraulic permeability.

The observed clinical tolerance to high solute and weight removal rates differs from the experience with rapid conventional haemodialysis and must be related to the only two fundamentally different features of our approach: bicarbonate dialysate and a high convective solute transport component.

The clinically demonstrated efficiency in this study opens new horizons to shorten treatment time. Treatments of well under two hours, equivalent in terms of total clearance of small and large solutes to conventional haemodialysis, are within reach.

References

Open Discussion

PORT (Michigan) This is very important progress that has been made. Do you find any difference in clinical tolerance for three different dialysers?

VON ALBERTINI To answer your question specifically we have not noticed differences between the three dialysers involved. I do not rule out that treatment tolerance is the multifactorial phenomenon. Among the two points I mentioned which is not really bicarbonate dialysis is absence of acetate and convective transport. I am sure membrane parameters will play a role and all these three membranes used have better biocompatibility. We also used PAN membranes in this study and found similar results.

SHALDON (Chairman) If you make the assumption that bicarbonate and biocompatibility perhaps are more important than convective transport what would be the effect of using those two classical diffusion membranes rather than combined convection and diffusion? Wouldn't that be a simpler system with less potential risk to the patient?

VON ALBERTINI Your comment is very well taken. The point I would like to make is using these very highly permeable membranes, thinner membranes in zero configuration, will always entail the necessary consequences of the flow resistance and transmembrane fluxes in both directions. Our configuration allows us to adequately control this, maximise ultrafiltration and at the same time provide a safe way of working with sterile dialysate with necessarily occurring back filtration.

SHALDON (Chairman) That just leads me to one very quick question. Your experience is limited in terms of numbers so obviously you have not had pyrogen reactions. We have been pouring dialysate into people's veins for years through filters, and I firstly would be concerned with using only one Amicon filter between the patient and your crude dialysate system preparing the fluid. Do you have any view on that?

VON ALBERTINI Well, my observation number may be limited for haemodiafiltration but I happen to have made about 80,000 litres of haemodiafiltration...
fluid which I have instilled into patients. The point is that you have double
security because the membrane you are using for the treatment itself acts as
the last filter and, in our experience, it is sufficiently safe to use an Amicon in
the dialysate part and then use the final filter as a second safety measure. We
have, by the way, always checked with limulus and cultures and found that it is
negative.

KESHAVIAH (Minneapolis) Do you have any experience with chronic exposure
using this form of therapy? Secondly, what was the needle you used? You
mentioned 14 gauge one inch, was it an Avon needle?

VON ALBERTINI No it was Drake Willock. I would love to have the needle
you have which is shorter but we have not been able to get it. Obviously the
only limit to increase efficiency is, in fact, the needle. I told you that we have
made flow measurement in accesses and it exceeds by far the rate that we are
using here. As far as chronic studies are concerned we have now six patients who
have undergone at least one month of this therapy. We have one patient who has
undergone eight weeks therapy.