Effect of ultrafiltration on peripheral urea sequestration in haemodialysis patients

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Abstract

Background. Ultrafiltration (UF) is assumed to enhance urea removal during haemodialysis (HD) because of convective transport and because of contraction of urea distribution volume. However, UF-induced blood volume reduction has been hypothesized to enhance peripheral urea sequestration and post-dialysis urea rebound (PDUR), possibly reducing HD effectiveness. The effect of UF on PDUR was investigated in this study.

Methods. Nine HD patients were studied on two subsequent treatment days. The first HD was performed with UF (UF-rate = 0.78 ± 0.27 l/h), and the second treatment without UF. Serial measurements of serum water urea nitrogen concentration, arterial blood pressures (BP), and relative blood volume changes (ΔBV%) were obtained over the duration of HD.

Results. BP and ΔBV% decreased with UF (BPsys = −9%, BPdia = −8%, BPmean = −9%, ΔBV% = −15%) but increased or remained unchanged without UF (BPsys = 9%, BPdia = 12%, BPmean = 11%, ΔBV% = 1%). PDUR was 28.6 ± 9.6% without UF, and increased in every single patient with UF (40.7 ± 13.2%, P < 0.01). Modelled perfusion of the peripheral low-flow compartment decreased from 1.45 ± 0.54 l/min without UF to 0.91 ± 0.42 l/min with UF (P < 0.05), thereby explaining an enhanced two-compartment effect and increasing PDUR.

Conclusion. The significant increase in the two-compartment effect of urea kinetics observed in current HD accompanied by UF can be explained by compensatory, intradialytic blood flow redistribution induced by blood volume reduction. Because of the link between UF and blood flow, limited solute clearance treatment modes that optimize fluid removal such as variable UF will also have favourable effects on delivered dose of dialysis.

Keywords: haemodialysis; isovolaemic haemodialysis; post-dialysis urea rebound; relative blood volume; ultrafiltration; urea kinetic modelling

Introduction

There are both primary and secondary effects of ultrafiltration (UF) on haemodialysis (HD) urea kinetics:

- Primary effects are defined as effects relating to the convective removal of urea with UF and contraction of urea distribution volume (V), thereby increasing dialysis efficiency (K/V).
- Secondary effects are defined as changes in the two-compartment effect which result from physiologic compensation to UF-induced blood volume reduction.

Primary effects of UF on HD, which are well documented and included in most mathematical models of urea kinetics, account for a significant but modest fraction of total urea removal [1,2]. Apart from primary effects of UF, the delivered dose of dialysis has been observed to depend on degrees of hydration, haemodynamic stability, and UF rates [3–5]. The secondary effect of UF on HD efficiency can be explained by the regional blood flow model where urea transport is assumed as largely blood flow limited [6]. It is well accepted that UF-induced blood volume reduction elicits compensatory peripheral vasoconstriction in stable HD patients [7]. Therefore, it can be hypothesized that reduced tissue perfusion may contribute to urea sequestration in peripheral compartments. Indeed, PDUR increased with UF in five of seven patients when dialysis was performed with UF compared with dialysis without UF [5]. However, combined effects of UF were not analysed by two-compartment urea kinetic modelling. Therefore, it was the aim of this study to provide a urea kinetic analysis.
of the effects of UF on PDUR in a series of HD treatments performed with and without UF.

Patients and methods

In each patient the study was performed on two consecutive treatment days, starting with a midweek dialysis. On the first treatment day, HD was performed with UF (protocol A) with prescribed dialysis duration (t) and extracorporeal blood flow (Q_b) while 48 h later, HD was repeated without UF (protocol B). In order to separate the clearance and the UF components of the standard HD treatment, the second dialysis treatment was split into an isovolaemic phase, during which HD was done without UF but with the same blood flow and dialysis duration prescribed for the regular treatment, followed by a 2-h rebound phase without HD and without UF, and by a final and variable UF and low efficiency HD phase when excess body water was removed to reach the prescribed target weight.

Bicarbonate based HD (Na^+ 143, K^+ 2, Ca^{2+} 3.5, Mg^{2+} 1, HCO_3^- 37, Cl^- 107, acetate 6 mEq/l, glucose 11 mmol/l) was delivered with a volumetrically balanced dialysis machine (2008E, Fresenius Medical Care, Walnut Creek, CA, USA). The effect of UF on relative blood volume changes was measured by a non-invasive optical technique (Crit-Line Instrument, In-Line Diagnostics, Riverdale, UT, USA) [8].

Pre-dialysis blood samples (c_pre) were taken from the access needle, intradialytic samples (c_intrad) were taken both from arterial (c_{intra,art}) and venous (c_{intra,ven}) blood lines. Intradialytic samples were drawn at hourly intervals at full blood flow. Post-dialysis samples were drawn from the arterial blood line at the very end of dialysis (c_{post,0}) and at 2, 5, 10, 20 and 30 min intervals. While c_{post,0} was sampled at full Q_b, subsequent samples (c_{post,2} and c_{post,3}) were sampled at low blood flow (Q_b < 70 ml/min) and with HD in bypass. The patient was disconnected from the extracorporeal circulation after having taken the 5 min sample. Thereafter, post-dialytic samples were drawn from the access needle.

Serum water urea nitrogen (SWUN) was determined by the urease/conductivity technique (BUN Analyzer 2, Beckman Instruments, Inc., Brea, CA, USA). The standard deviation (SD) for repeated SWUN measurements was ±1 mg/100 ml. Plasma water Na^+ was measured electrochemically (Ionometer, Fresenius Medical Care, Bad Homburg v.d.H., Germany).

Patients had given informed consent to participate in this study.

Analysis

The effect of UF on urea kinetics was measured by post-dialysis urea rebound (PDUR)

$$PDUR = \frac{c_{post,0} - c_{post,30}}{c_{post,0}},$$

by the patient clearance time (t_p) [9] given in minutes which is calculated from the post-dialysis urea rebound according to

$$t_p = \left(\frac{\ln c_{eq} / c_0}{\ln c_{eq} / c_0 - 1}\right) \cdot 60,$$

where c_{eq} refers to a 30 min post-dialytic sample, corrected for continuing urea generation rate (c_{eq} = 0.93 \times c_{post,30}); from the difference between single pool K_d/V (K_d/V_{sp}) from a linearized formula [10] and equilibrated single-pool

$$K_t/V (K_t/V_{sp})$$

derived for the average dialysis patient from K_d/V_{sp} and the clearance rate [11]

$$\kappa = t \cdot \frac{(K_t/V_{sp} - K_t/V_{eq}) - 0.03}{K_t/V_{sp}}$$

where κ is the slope of the rate-equation given in hours [11]; and by parameter identification based on regional blood flow urea kinetic modelling as described previously [12].

Regional blood flow model

In the regional blood flow model, 20% of total body water is assumed to be located in the high-flow compartment representing the internal organs and the brain, which receive 80% of systemic blood flow. The remainder of body water, under resting conditions, is perfused by a very small fraction of the systemic blood flow. The differences in mean specific perfusion (ml/min/kg tissue water) between combined body compartments and the assumption that urea exchange in the microvasculature is mostly flow limited offers a physiologic explanation for peripheral urea sequestration during HD and post-dialytic urea rebound in HD patients. In addition to providing a physiologic approach that can explain typical degrees of urea sequestration and rebound, the model also can account for variability of peripheral urea sequestration and post-dialytic urea rebound as may be observed with manoeuvres such as intradialytic exercise [13], high dialysate sodium concentrations [14], high dialysate potassium concentrations [15] and local heating [16].

Two parameters of the regional blood flow model, post-dialysis urea distribution volume (V) and the fractional perfusion of the low flow compartment (f_{Q_b}) were identified by fitting modelled intra- and post-dialytic SUN concentrations to experimental concentrations as described previously [17]. Blood side dialyser clearance (K_d) was determined from paired dialyser inflow and outflow SUN concentrations and extracorporeal blood flows (Q_b) and corrected for a fractional blood urea distribution of 85%. Model parameters were assumed as described previously. The fitting procedure was performed with the Solver option provided by Microsoft Excel 5.0 minimizing the sum of squared errors between experimental and modelled data. Because of the relative importance of the rebound data, the fitting procedure was constrained to allow for a 2% deviation between fitted and experimental c_{post,0} and c_{post,30} concentrations.

Statistical analysis

The relative change of a value X(ΔY%) between times t = 0 and t = 1 or the relative difference of a value between protocols A and B was calculated as (X_t/X_0 − 1) × 100, and (X_A/X_B − 1) × 100, respectively. Data are presented as mean ± SD. Differences between groups were compared by a non-parametric test (Wilcoxon signed rank test) and a probability of P < 0.05 was considered significant. Correlation between parameters was studied by linear regression analysis and analysis of variance (ANOVA).

Results

Mean patient and treatment data in nine study patients are given in Table 1. Treatment times (199 ± 30 min, range 150–240 min) and dialyser clearances were the same for both protocols. As expected for the average
weekly SWUN profile, pre-dialysis SWUN concentrations tended to be higher with protocol A (55.3 ± 18.8 mg/100 ml) done midweek than protocol B (49.5 ± 14.6 mg/ml) carried out later in the week (P = n.s.). Equilibrated post-dialysis SWUN concentrations as well as the absolute changes in post-dialysis

Table 1. Mean patient and treatment data (n = 9)

<table>
<thead>
<tr>
<th></th>
<th>HD with UF protocol A</th>
<th>HD only protocol B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, pre (kg)</td>
<td>83.6 ± 24.0</td>
<td>84.2 ± 24.0</td>
</tr>
<tr>
<td>Body weight, post (kg)</td>
<td>81.0 ± 23.7</td>
<td>84.1 ± 24.0</td>
</tr>
<tr>
<td>UFR (l/h)</td>
<td>0.78 ± 0.27</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>K_d, diffusive (ml/min)</td>
<td>308 ± 44</td>
<td>309 ± 42</td>
</tr>
<tr>
<td>K_d, diffusive and convective (ml/min)</td>
<td>320 ± 43</td>
<td>310 ± 42</td>
</tr>
<tr>
<td>Time (min)</td>
<td>199 ± 30</td>
<td>199 ± 30</td>
</tr>
<tr>
<td>c_pre (mg/100 ml)</td>
<td>55.3 ± 18.8</td>
<td>49.5 ± 14.6</td>
</tr>
<tr>
<td>c_post (mg/100 ml)</td>
<td>14.6 ± 9.2</td>
<td>12.7 ± 7.0</td>
</tr>
<tr>
<td>c_equ (mg/100 ml)</td>
<td>18.5 ± 10.7</td>
<td>14.9 ± 7.6</td>
</tr>
<tr>
<td>c_equ – post (mg/100 ml)</td>
<td>4.0 ± 2.0</td>
<td>2.2 ± 1.3</td>
</tr>
</tbody>
</table>

Ultrafiltration rate (UFR); dialyser clearance (K_d); serum water urea nitrogen concentration (c) pre-dialysis (pre), at the end of haemodialysis (post), and equilibrated at the end of post-dialysis rebound (eq).

Table 2. Blood pressures and relative blood volume changes (n = 9)

<table>
<thead>
<tr>
<th></th>
<th>HD with UF protocol A</th>
<th>HD only protocol B</th>
</tr>
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<tbody>
<tr>
<td>BP_syst pre (mmHg)</td>
<td>149 ± 21</td>
<td>147 ± 23</td>
</tr>
<tr>
<td>BP_diast pre (mmHg)</td>
<td>83 ± 14</td>
<td>82 ± 12</td>
</tr>
<tr>
<td>BP_mean pre (mmHg)</td>
<td>105 ± 16</td>
<td>104 ± 15</td>
</tr>
<tr>
<td>BP_syst post (mmHg)</td>
<td>135 ± 21</td>
<td>158 ± 21</td>
</tr>
<tr>
<td>BP_diast post (mmHg)</td>
<td>74 ± 14</td>
<td>91 ± 11</td>
</tr>
<tr>
<td>BP_mean post (mmHg)</td>
<td>94 ± 16</td>
<td>114 ± 13</td>
</tr>
<tr>
<td>ΔBV% (%)</td>
<td>-15.0 ± 7.0</td>
<td>0.8 ± 2.5</td>
</tr>
<tr>
<td>[Na⁺] pre (mEq/l)</td>
<td>150 ± 4</td>
<td>153 ± 4</td>
</tr>
<tr>
<td>[Na⁺] post (mEq/l)</td>
<td>157 ± 3</td>
<td>156 ± 3</td>
</tr>
<tr>
<td>[Na⁺] post−pre (mEq/l)</td>
<td>4.5 ± 3.1</td>
<td>2.2 ± 1.6</td>
</tr>
</tbody>
</table>

Blood pressure (BP); relative blood volume change (ΔBV%).

Table 3. Urea kinetic data (n = 9)

<table>
<thead>
<tr>
<th></th>
<th>HD with UF protocol A</th>
<th>HD only protocol B</th>
</tr>
</thead>
<tbody>
<tr>
<td>K_t/V_equ</td>
<td>1.68 ± 0.35</td>
<td>1.56 ± 0.29</td>
</tr>
<tr>
<td>K_t/V_equo</td>
<td>1.30 ± 0.26</td>
<td>1.29 ± 0.22</td>
</tr>
<tr>
<td>K_t/V_modelled</td>
<td>1.51 ± 0.34</td>
<td>1.44 ± 0.28</td>
</tr>
<tr>
<td>V_modelled (l)</td>
<td>36.4 ± 5.5</td>
<td>38.3 ± 4.5</td>
</tr>
<tr>
<td>f/Ω_L</td>
<td>0.15 ± 0.06</td>
<td>0.24 ± 0.10</td>
</tr>
<tr>
<td>Q_L (min)</td>
<td>0.91 ± 0.42</td>
<td>1.45 ± 0.54</td>
</tr>
<tr>
<td>PDUR (%)</td>
<td>40.7 ± 13.2</td>
<td>28.6 ± 9.6</td>
</tr>
<tr>
<td>k (slope) (h)</td>
<td>-0.80 ± 0.21</td>
<td>-0.65 ± 0.21</td>
</tr>
<tr>
<td>t_p (min)</td>
<td>45 ± 16</td>
<td>28 ± 14</td>
</tr>
</tbody>
</table>

Urea clearance (K); time (t); urea distribution volume (V); single pool K_t/V (K_t/V_eq); equilibrated single pool K_t/V (K_t/V_eqo); fraction of systemic blood flow perfusing the low flow system (f/Ω_L); blood flow perfusing the low flow system (Q_L); post dialysis urea rebound (PDUR); slope of the rate equation (k); patient clearance time (t_p).

SWUN concentrations measured as c_equ−c_post were higher when treatments were accompanied by UF (protocol A) (P < 0.05).

Pre-dialysis systolic, diastolic and mean arterial pressures were not different between groups; however, when accompanied by UF (protocol A), blood pressures dropped during HD, while blood pressures increased during HD without UF (protocol B), the differences between groups being significant (P < 0.01) (Table 2). With UF (protocol A) blood volume dropped by −15.0 ± 7.0%. Blood volume slightly increased (0.8 ± 2.5%) without UF (protocol B). Plasma sodium concentrations were comparable with both protocols and increased during HD.

Although there was a trend for higher equilibrated K_t/V (K_t/V_eqo) and modelled K_t/V (K_t/V_modelled) in the group in which diffusive solute removal was accompanied by convective solute removal because of UF (protocol A), differences between groups were not significant (Table 3). Single pool K_t/V (K_t/V_eq) was significantly higher in the patients with UF because effects of variable rebound are not considered in the single compartment approach.

When data were analysed by urea kinetic modelling, i.e. parameter identification of the regional blood flow model, modelled blood flow (Q_L) to the low flow compartment was identified to have significantly decreased during HD with UF (protocol A) when compared with HD done without UF (Table 3). Modelled Q_L decreased from 1.45 ± 0.54 l/min without UF to 0.91 ± 0.42 l/min with UF (P < 0.05). PDUR increased from 28.6 ± 9.6% without UF to 40.7 ± 13.2% with UF (P < 0.01). The increase in PDUR was observed in every single patient. Other measures of the two-compartment effect such as the patient clearance time t_p [9] or the slope k of rate-equation [11] also increased with UF.

Discussion

Analysis of experimental data collected during HD carried out with and without UF showed that apart from the primary effect of UF, which refers to convective removal of urea and volume contraction, there is a physiologic component which appears to affect the two-compartment nature of urea kinetics. The observed increase in post-dialysis urea rebound in each dialysis performed with UF can be explained by increased urea sequestration in the peripheral compartment of the regional blood flow model. It is plausible to assume that this sequestration is caused by reduced peripheral perfusion occurring with UF-induced blood volume reduction, especially as a decrease in cardiac output and an increase in systemic vascular resistance is commonly observed with HD and UF [18].

PDUR is an indirect measure of the two-compartment behaviour of urea. It is largely independent of dialysis duration [19] but it increases with dialysis.
efficiency \((K/V)\). Dialysis efficiency increases with UF because of convective solute removal (higher \(K\)) and because of total body water volume contraction (smaller \(V\)) [2]. Thus, a small increase in PDUR could be explained by an increase in HD efficiency. On the other hand, if regional perfusion were assumed to remain unchanged during UF, specific tissue perfusion would increase, and peripheral urea sequestration would be reduced. As a consequence, a small decrease in PDUR would be expected with increasing fluid removal and constant specific perfusion. Clearly, this is not the case.

The combined result of both primary and secondary effects of UF can be analysed by the regional blood flow model [6]. As suggested by the significant increase in PDUR a reduction in specific tissue perfusion was assumed with UF. This is in accordance with data presented elsewhere [18]. In this analysis we chose to model a reduction in the perfusion of the low flow system \((Q_L)\) thereby reducing flow limited peripheral urea removal and enhancing the two-compartment effect (Figure 1).

Relation to other measures of the two-compartment effect

Recently, the two-compartment effect has been quantitated by relationships intended to predict equilibrated, post-dialysis urea concentration [9] or to correct single pool \(Kt/V\) for two-compartment effects [11]. These relationships were derived from the observation that the two-compartment effect was rather uniform in the standard dialysis patient treated within a wide range of low to high efficiency procedures utilizing standard dialysate compositions and constant UF rates with patients resting in a recumbent body position.

In the approach by Tattersall et al. [9] the constant two-compartment effect was described by the patient clearance time \((t_p = 30\) min), which is calculated from Equation 2. In this study, \(t_p\) was higher in UF treatments \((45 \pm 16\) min) and lower in isovolaemic treatments \((28 \pm 14\) min). Overall, \(t_p\) increased with the degree of the two-compartment effect. In the approach by Daugirdas et al. [11] the degree of the two-compartment effect was given by the slope of the rate-equation \((\kappa)\) which can be calculated from Equation 3. In the data obtained in this study, absolute slopes were steeper in UF treatments \((-0.80 \pm 21\) h) than in isovolaemic treatments \((-0.65 \pm 0.21\) h).

Comparison with published data for \(t_p\) (30 min) and \(\kappa\) \((-0.65\) h) showed a 50 and 23\% deviation for \(t_p\) and \(\kappa\), respectively. However, the difference was not significant (one-sample sign test) and published values for \(t_p\) and \(\kappa\) to estimate the effect of urea dysequilibrium appear to be valid also in view of this study.

Conclusion

In all patients HD with UF increased PDUR when compared with isovolaemic HD. The regional blood flow model offers a physiologic interpretation of this observation where hypovolaemic compensation reduces peripheral blood flow thereby increasing peripheral urea sequestration. From the clinical point of view it follows that two main aspects of HD, clearance and UF, are not independent from each other, also on a physiologic basis. The relationship becomes more important as treatment times are reduced and UF rates are increased. Switching from constant to variable UF modes such as using high initial and subsequently decreasing UF rates is likely to have positive effects both on UF-induced blood volume reduction [20] and on dialysis efficiency.

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References


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