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Removal of water-soluble and protein-bound solutes with reversed mid-dilution versus post-dilution haemodialfiltration

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Abstract

Background. Convective dialysis strategies are superior in the removal of protein-bound uraemic retention solutes. Mid-dilution and mixed-dilution haemodiafiltration (HDF), both combining pre-dilution and post-dilution, are promising options to further improve removal capacity and have been shown of additional benefit for large middle molecules. In this study, we compared the removal of small water-soluble and protein-bound solutes in post-dilution versus mid-dilution HDF.

Methods. Fourteen chronic haemodialysis (HD) patients were included in this crossover study. Patients were kept for 4 weeks on high-flux HD. On the mid-week session of Weeks 3 and 4, either post-dilution or reversed mid-dilution HDF were applied, in random order. Blood and dialysate flows were maintained at 300 and 800 mL/min, while the substitution flow was 75 mL/min in post-dilution and 150 mL/min in mid-dilution HDF. Based on the data collected during the sessions under study, extraction ratio (ER) and reduction ratio (RR) of small water-soluble and protein-bound solutes were calculated, as well as total solute removal (TSR) based on spent dialysate.

Results. No differences were observed for TSR, ER and RR for protein-bound solutes. For small water-soluble solutes, ER in post-dilution HDF was significantly higher than in mid-dilution HDF: 0.92 ± 0.02 versus 0.87 ± 0.04 for urea (P < 0.001), 0.92 ± 0.02 versus 0.88 ± 0.02 for creatinine (P < 0.001) and 0.84 ± 0.02 versus 0.82 ± 0.03 for uric acid (P = 0.009). TSR and RR were, however, not different due to the lower inlet concentrations with post-dilution HDF.

Conclusions. TSR of mid-dilution and post-dilution HDF was not different for both small water-soluble and protein-bound compounds. Both strategies in the setting as applied in this study are as adequate for the removal of these solutes.

Keywords: adequacy; haemodiafiltration; mid-dilution; protein-bound; solute removal

Introduction

Almost 100 uraemic retention solutes have been identified, which is probably a minority of the wide range of uraemic toxins accumulating during chronic renal failure and contributing to the uraemic syndrome [1, 2]. It is generally accepted that increasing dialyser pore size results in a better removal of larger peptidic solutes (so-called middle molecules), which in turn has been linked to improved survival [3, 4]. Adding convection to this approach has been associated with better removal [5–7] and survival in observational studies [8–10] but also in a small controlled trial [11].

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Protein-bound solutes, although mostly having a low molecular weight, are difficult to remove. This is mainly due to their binding to larger proteins with a molecular weight beyond the cut-off of currently used high-flux membranes. Several studies indicate that convective strategies, such as haemodiafiltration (HDF), are more efficient in removing these toxins [12–14]. This removal is important as several protein-bound solutes have been linked to inflammation, vascular disease and mortality [15–26].

Post-dilution HDF enhances the removal of large solutes such as β2M, compared to pre-dilution HDF. This is attributable to the absence of dilution of blood with the post-dilution strategy. For the removal of protein-bound solutes, however, no differences were observed in removal between both strategies [13]. In addition, pre-dilution HDF also has a number of advantages, such as less restriction to increase convective transport, as well as relatively lower transmembrane pressure, reducing the risk for clotting, clogging and albumin loss [27]. In the search for the optimal convective therapy, mid-dilution and mixed-dilution HDF have been introduced with the intention to combine the most important advantages of both strategies since they allow simultaneous infusion in a pre-dilution and post-dilution mode. In mid-dilution, blood is flowing consecutively through the inner and outer fibres of the dialyser, respectively, and is diluted at the U-turn. In the mixed-dilution mode, blood is flowing through the dialyser as normal and is diluted at the inlet and outlet. These strategies were superior in the removal of middle molecules compared to standard haemodialysis (HD) and post-dilution HDF [28, 29]. Clinical data on the removal of protein-bound solutes are, however, lacking.

In the present study, we investigated the difference in removal of small water-soluble (urea, creatinine and uric acid) and protein-bound solutes [hippuric acid, indole-3-acetic acid, indoxyl sulphate, p-creglycol sulphate and 3-carboxyl-4-methyl-5-propyl-2-furanpropionic acid (CMPF)] between post-dilution and mid-dilution HDF by evaluating the extraction ratio (ER), total solute removal (TSR) and the reduction ratio (RR).

### Materials and methods

#### HDF modes

Online HDF is a renal replacement therapy that combines diffusion and convection in a standard high-flux dialyser, maintaining the fluid balance by substitution of ultrafiltrate with a non-propyrogenic solution. The substitution fluid can be added either at the dialyser blood inlet (pre-dilution) or at the outlet (post-dilution) or as a combination of pre- and post-dilution (mixed dilution). With pre-dilution and post-dilution HDF, typical substitution fluid flows are, respectively, 50 and 25% of the blood flow.

Mid-dilution HDF can be performed using a specially designed dialyser. In the reversed mid-dilution set-up used in the present study, blood is first flowing through the inner fibres of the dialyser where post-dilution occurs, before it flows back in the outer fibres after having been submitted to pre-dilution. The dialysate flow is countercurrent and co-current, respectively, with respect to the blood flow in the inner and outer fibres.

#### Patients

Exclusion criteria were active infection, pregnancy, unstable clinical condition and known coagulation problems.

This study included 14 chronic kidney disease patients (11 males, 3 females, age 70 ± 11 years, body weight 78 ± 18 kg, haematocrit 36.7 ± 3.6, Kt/V according to Daugirdas et al. [30] of 1.70 ± 0.34 at the study start, six central venous catheters and eight fistulas as vascular access and 40 ± 19 months on dialysis) (see Table 1), who were on thrice weekly HDF for 40 ± 19 months (5–72 months). They were routinely dialysed with a blood flow of 343 ± 18 mL/min (Qf = 300–350 mL/min) in post-dilution HDF mode with either FX800 (Fresenius Medical Care, Germany) (n = 9), Polyflux 170H (Gambro, Sweden) (n = 2), Xenium 210 (Baxter) (n = 2) or Phylter 17SD (Bellco, Italy) (n = 1) dialysers (see Table 2). All patients had a permanent vascular access allowing a dialyser blood flow of >300 mL/min (eight fistulas and six central venous catheters).

The study was approved by the local Ethics Committee and conducted in accordance with the principles of the Declaration of Helsinki and rules of Good Clinical Practice. Written informed consent was obtained from all participants.

#### Study design

This prospective crossover study started with a washout period of 2 weeks during which all patients underwent high-flux HD with a Phylter HF 17G (1.7 m²) (Bellco, Italy) at a blood flow of 300 mL/min and a dialysate flow of 800 mL/min. In the following 2 weeks, the same dialysis strategy was continued, but at each of the two mid-week sessions, HD was switched to either post-dilution HDF or reversed mid-dilution HDF.

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics&lt;sup&gt;a&lt;/sup&gt;</th>
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<tr>
<td><strong>Patient</strong></td>
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<td>Mean</td>
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<td>SD</td>
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<sup>a</sup>BW, body weight; Hct, haematocrit; Kt/V according to the second generation single pool Kt/V defined by Daugirdas et al. [30]; C<sub>urea</sub>, urea predialysis concentration; Qf, blood flow; n.a., not applicable.
HDF, in random order, without change in blood flow and dialysate flow. Post-dilution HDF was performed with Phylter HF 22SD dialysers (2.2 m²) (Bellco, Italy) and a substitution flow of 75 mL/min (25% of blood flow rate). Reversed mid-dilution HDF (OLpur MD220 dialyzer) was performed with a substitution flow of 150 mL/min (50% of blood flow rate). Since substitution fluid forms part of the dialysate flow, effective dialysate flow rates were 725 and 650 mL/min with post-dilution and mid-dilution HDF, respectively. Dialyser characteristics are given in Table 2.

All experimental sessions were performed with Fresenius 5008 dialysis machines. The anticoagulation (tinzaparin 4500E (n = 6), 3500E (n = 2), 5000E (n = 1) and 6000E (n = 1) (Innohep®; Leo Pharma, The Netherlands) and enoxaparin 60 mg (n = 3) and 40 mg (n = 1) (Clexane; Sanofi–Aventis, France)] and the length of dialysis were continued as usual; ultrafiltration was defined depending on interdialytic body weight gain.

**Sampling and measurements**

During the sessions under study, (transmembrane) pressure alarms were recorded to check feasibility of both HDF techniques. Furthermore, blood was sampled from the inlet needle or bloodline before starting the blood pump (pre-dialysis) and exactly 15 s after setting the blood pump (pre-dialysis). Blood was also sampled from the dialyser inlet and outlet bloodline at 60 min, without slowing down the pump flow. In the post-dilution mode, outlet blood samples were collected downstream from the substitution fluid infusion site. Spent dialysate collection was performed with a validated technique using a droplet pump to get a dialysate sample which has a concentration that is representative for the concentration of the entire volume of spent dialysate.

During dialysate collection and after blood collection, samples were placed on ice. Blood samples were centrifuged (3000 rpm corresponding to 1250 g) and stored at −80°C until analysis. Urea (MW: 60 Da) and creatinine (113 Da) were measured by standard laboratory methods. Analysis of uric acid (168 Da) was performed by reversed-phase high-performance liquid chromatography (RP-HPLC) with ultraviolet (UV) detection at 254 nm. To establish the total concentration of hippuric acid detection was performed with a validated technique using a droplet pump for the concentration of the entire volume of spent dialysate.

For the small water-soluble solutes urea, creatinine and uric acid. Also the corresponding outlet concentrations during post-dilution HDF compared to mid-dilution HDF with mid-dilution HDF.

**Calculations**

The dialyser ER (dimensionless) was calculated as the relative change in concentration from the dialyser inlet (Cpre) towards the outlet (Cpost):

\[
ER = \frac{C_{\text{inlet}} - C_{\text{outlet}}}{C_{\text{inlet}}} \quad (1)
\]

TSR (milligram) was calculated from spent dialysate concentration at the end of dialysis (CD,end) multiplied by the total volume of dialysate (VD,end):

\[
\text{TSR (mg)} = V_{\text{D,end}} \times C_{\text{D,end}} \quad (2)
\]

RR (%) of solutes was defined as a function of pre-dialysis (Cpre) and post-dialysis concentrations (Cpost) of samples collected from the inlet bloodline:

\[
\text{RR (\%)} = \frac{C_{\text{pre}} - C_{\text{post}}}{C_{\text{pre}}} \times 100 \quad (3)
\]

For the protein-bound compounds, concentration at the dialysis end (Cpost) was corrected for haemocomcentration by a factor (F) based on TP concentration at start versus end of the dialysis session: \( F = \frac{TP_{\text{pre}}}{TP_{\text{post}}} \). Likewise, dialysate outlet concentration (Coutlet) was corrected by \( F = \frac{TP_{\text{inlet}}}{TP_{\text{outlet}}} \).

**Statistical analysis**

Data are expressed as mean ± SD. Statistical analyses were carried out using the parametric t-test or non-parametric Wilcoxon Signed-rank test for paired samples. A P ≤ 0.05 was considered to be statistically significant. All statistical analyses were performed using PASW Statistics 18 (SPSS Inc., Chicago, IL) for Windows (Microsoft Corp, Redmond, WA).

**Results**

During the test sessions with mid-dilution HDF, as with post-dilution HDF, there were no pressure alarms. The post-dilution and mid-dilution HDF sessions lasted for 249 ± 15 and 251 ± 17 min [non significant (n.s.)] with net ultrafiltration rates of 7.7 ± 3.9 mL/min and 6.7 ± 4.1 mL/min (n.s.) and processed blood volumes of 72 ± 4 L and 72 ± 5 (n.s.).

Table 3 reports the measured pre-dialysis (Cpre), post-dialysis (Cpost), dialyser inlet at 60 min (Cinlet), dialyser outlet at 60 min (Coutlet) and spent dialysate concentrations (CD,end) for the solutes under study. Blood inlet concentrations, as taken at 60 min, were significantly lower during post-dilution HDF compared to mid-dilution HDF for the small water-soluble solutes urea, creatinine and uric acid. Also the corresponding outlet concentrations were lower for post-dilution HDF. None of the other values were different. Of note there were no differences in concentration pre- and post-dialysis between both modalities, both inlet and outlet values were higher with mid-dilution HDF.

To calculate the different dialysis adequacy parameters, post-dialysis as well as outlet concentrations were corrected according to different factors which were derived from TP concentrations as reported in Table 2. Calculated ERs, TSRs and RR are reported in Table 5. Dialyser ER was significantly higher with post-dilution HDF compared to mid-dilution HDF for the small water-soluble solutes: urea (0.92 ± 0.2 versus 0.87 ± 0.4; P < 0.001), creatinine (0.92 ± 0.2 versus 0.88 ± 0.2; P < 0.001)
and uric acid (0.84 ± 0.2 versus 0.82 ± 0.3; P = 0.009). No differences in ER were found for the protein-bound solutes. TSR and RR were not significantly different between the post-dilution and mid-dilution HDF sessions for all solutes under study.

Figure 1 shows the concentration decrease during post-dilution and mid-dilution HDF for urea, creatinine and uric acid.

**Discussion**

While most studies comparing different convective strategies focus on middle molecule removal, we investigated the removal of protein-bound solutes with post-dilution and mid-dilution HDF. Fourteen patients were enrolled in a crossover study and dialysed in random order with post-dilution or mid-dilution HDF during two consecutive mid-week sessions.

The most important result of this study is that TSR, dialyser ER and RR of protein-bound solutes were not different for both options. For the water-soluble solutes, ER was slightly but significantly higher with post-dilution HDF while also no differences were observed for TSR and RR. This higher ER for post-dilution HDF while RR and TSR were not different is a seemingly contradictory finding. In Figure 1, it can be seen that dialyser inlet concentrations at 60 min after the dialysis start were significantly lower with post-dilution HDF compared to mid-dilution HDF, while this was not the case at the start and the end of dialysis. Hence, it seems that plasma concentrations are decreasing faster at the start of post-dilution HDF. We hereby hypothesize that this is due to the higher ER and due to the retardation of transport in the patient from extravascular to vascular compartments. This trend is, however, neutralized during the subsequent part of the dialysis session. A possible explanation might be that the vascular compartment is refilled by transport from the extravascular compartment, which will be more substantial if plasma concentration is lower. This phenomenon might finally result in equal RR’s for post-dilution and mid-dilution HDF. In addition, lower plasma concentrations at the dialyser inlet will result in lower mass removal via the dialyser and consequently smaller concentrations in the spent dialysate. This might possibly explain why TSR with post-dilution HDF was not superior to mid-dilution HDF. Hence, the advantage of higher ERs to increase adequacy seems to be influenced by the dialysis duration and the solute distribution in the patient’s body.

Up till now, most studies dealing with mid-dilution HDF focused on the removal of small molecules like urea, creatinine and phosphorus on the one hand and middle molecules like β2M on the other [28, 29, 32–34]. The strength of our study lies in the quantification of the removal of protein-bound solutes in mid-dilution HDF, solutes which even have been linked to inflammation, vascular disease and mortality [15–26].

Up to now, only three studies evaluated the removal of protein-bound solutes in HDF mode [13, 35, 36]. Bammens et al. [35] compared the removal of p-cresol during high-flux HD, post-dilution HDF (20 L) and pre-dilution HDF, the latter at low (20 L) and at high substitution volumes (60 L), and did not find a difference in

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**Table 3. Measured concentrations of solutes under study for post-dilution and mid-dilution HDF**

<table>
<thead>
<tr>
<th>Solute</th>
<th>Post-HDF</th>
<th>Mid-HDF</th>
<th>Post-HDF</th>
<th>Mid-HDF</th>
<th>Post-HDF</th>
<th>Mid-HDF</th>
<th>Post-HDF</th>
<th>Mid-HDF</th>
<th>Post-HDF</th>
<th>Mid-HDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>119 ± 27</td>
<td>116 ± 25</td>
<td>8.4 ± 2.2</td>
<td>8.4 ± 2.3</td>
<td>6.8 ± 1.0</td>
<td>7.0 ± 0.9</td>
<td>5.5 ± 4.9</td>
<td>5.6 ± 4.8</td>
<td></td>
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<tr>
<td>Ccreatine</td>
<td>29 ± 14</td>
<td>32 ± 14</td>
<td>2.7 ± 0.9</td>
<td>2.7 ± 1.0</td>
<td>1.7 ± 0.5</td>
<td>1.7 ± 0.4</td>
<td>1.4 ± 1.2</td>
<td>1.5 ± 1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cinlet</td>
<td>56 ± 20</td>
<td>67 ± 23*</td>
<td>4.3 ± 1.6</td>
<td>4.8 ± 1.6*</td>
<td>3.1 ± 1.1</td>
<td>3.6 ± 0.8*</td>
<td>2.6 ± 2.5</td>
<td>3.1 ± 2.6</td>
<td></td>
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<tr>
<td>Ccrea3</td>
<td>5 ± 2</td>
<td>9 ± 4*</td>
<td>0.33 ± 0.12</td>
<td>0.60 ± 0.26*</td>
<td>0.47 ± 0.14</td>
<td>0.65 ± 0.19*</td>
<td>0.83 ± 0.69</td>
<td>1.1 ± 0.8</td>
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<tr>
<td>Ccrea2</td>
<td>17 ± 6</td>
<td>16 ± 6</td>
<td>0.63 ± 0.30</td>
<td>0.60 ± 0.31</td>
<td>0.52 ± 0.15</td>
<td>0.50 ± 0.13</td>
<td>0.41 ± 0.36</td>
<td>0.39 ± 0.32</td>
<td></td>
<td></td>
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<tr>
<td>Indole-3-acetic acid</td>
<td>20 ± 1.0</td>
<td>21 ± 1.1</td>
<td></td>
<td></td>
<td>3.1 ± 1.5</td>
<td>3.2 ± 1.4</td>
<td>0.51 ± 0.34</td>
<td>0.53 ± 0.35</td>
<td></td>
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<tr>
<td>Indoxyl sulphate</td>
<td>1.1 ± 0.5</td>
<td>1.2 ± 0.6</td>
<td></td>
<td></td>
<td>1.9 ± 1.0</td>
<td>2.0 ± 0.9</td>
<td>0.53 ± 0.36</td>
<td>0.55 ± 0.41</td>
<td></td>
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<tr>
<td>p-Cresylsulphate</td>
<td>1.4 ± 0.6</td>
<td>1.7 ± 0.9</td>
<td></td>
<td></td>
<td>2.4 ± 1.2</td>
<td>2.6 ± 1.1</td>
<td>0.51 ± 0.33</td>
<td>0.54 ± 0.36</td>
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<tr>
<td>CMIF</td>
<td>0.06 ± 0.03</td>
<td>0.1 ± 0.2</td>
<td></td>
<td></td>
<td>2.2 ± 1.1</td>
<td>2.4 ± 1.1</td>
<td>0.53 ± 0.37</td>
<td>0.56 ± 0.38</td>
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</table>

*P < 0.05 between post-dilution and mid-dilution HDF.

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**Table 4. TP (g/L) in post-dilution and mid-dilution HDF**

<table>
<thead>
<tr>
<th>TP</th>
<th>Post-HDF</th>
<th>Mid-HDF</th>
</tr>
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<tbody>
<tr>
<td>TP&lt;sub&gt;pre&lt;/sub&gt;</td>
<td>61.8 ± 4.0</td>
<td>62.9 ± 5.5</td>
</tr>
</tbody>
</table>

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TSR when using post-dilution or pre-dilution HDF, irrespective of the substitution volume. High-volume pre-dilution HDF was, however, found superior compared to high-flux HD. Meert et al. [13] compared post-dilution and pre-dilution HDF and pre-dilution HF for different protein-bound solutes and found that post-dilution and pre-dilution HDF are equally superior to pre-dilution HF, suggesting that diffusion of the free fraction of the low-molecular weight protein-bound solutes is the most important removal mechanism with a relatively minor role for convection. Furthermore, solute removal with post-dilution and pre-dilution HDF was found similar. This is possibly due to the fact that the decrease of diffusion in the diluted blood is compensated by an increase of diffusion caused by the equilibrium shift of PB increasing the available free fraction. Susantitaphong et al. [36] investigated p-cresol removal in a mid-dilution HDF set-up by placing two small dialysers (1.1 m²) in series with dilution (300 mL/min) in between both dialysers and compared it with post-dilution HDF (substitution flow of 120 mL/min) and pre-dilution HDF (substitution flow of 330 mL/min). They found higher p-cresol clearances with mid-dilution HDF compared to post-dilution HDF, while no differences were observed between mid-dilution and pre-dilution HDF. The contrast with the findings presented here might be attributed to the fact that Susantitaphong et al. had countercurrent blood and dialysate flows in both dialysers, while this is not the case in the OLpur MD220 dialyzer that we used. Hence, the combination of countercurrent and co-current dialysate flows in the OLpur MD220 induces a small loss of dialysis efficiency.

Since the real mechanism behind the removal of protein-bound solutes remains partially undefined, it was interesting to investigate protein-bound solute removal during mid-dilution HDF, which can be seen as a combination of pre-dilution and post-dilution HDF. Since we performed mid-dilution HDF with a substitution flow rate of 50% of the blood flow rate, the same as was used by Meert et al. [13] for the pre-dilution HDF sessions, it could be assumed that in accordance with the results of Meert et al., no differences in TSR would be found comparing post-dilution with mid-dilution HDF. Our results confirm this assumption. Future studies, however, should be performed to unravel whether further increasing ultrafiltration and substitution flow rate in mid-dilution HDF could result in higher removals compared to post-dilution HDF, since probably the optimal ultrafiltration capacity has not been reached in the setting we applied.

Table 5. ER (−), TSR (mg, except for urea in g), RR (%) and corresponding P-values for post-dilution and mid-dilution HDF.

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>ER</th>
<th>TSR</th>
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<tr>
<td>Urea</td>
<td></td>
<td>Post</td>
<td>Mid</td>
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<tr>
<td></td>
<td></td>
<td>76.9 ± 8.5</td>
<td>73.6 ± 10.4</td>
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<tr>
<td>CREA</td>
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<td>68.4 ± 6.9</td>
<td>68.0 ± 7.3</td>
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<tr>
<td>UA</td>
<td></td>
<td>75.4 ± 5.3</td>
<td>75.2 ± 4.1</td>
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<tr>
<td>HA</td>
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<td>70.4 ± 1.35</td>
<td>70.6 ± 1.35</td>
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<tr>
<td>IAA</td>
<td></td>
<td>49.5 ± 7.4</td>
<td>49.4 ± 6.4</td>
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<tr>
<td>IS</td>
<td></td>
<td>48.7 ± 10.0</td>
<td>47.4 ± 8.2</td>
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<tr>
<td>PCS</td>
<td></td>
<td>44.0 ± 8.4</td>
<td>42.7 ± 7.2</td>
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<tr>
<td>CMPF</td>
<td></td>
<td>5.5 ± 11.1</td>
<td>4.4 ± 9.1</td>
</tr>
</tbody>
</table>

*CREA, creatinine; HA, hippuric acid; IAA, indole acetic acid; IS, indoxyl sulphate; PCS, p-cresylsulphate; UA, uric acid; n.a., not applicable.

*P < 0.05 between post-dilution and mid-dilution HDF.

![Fig. 1](image-url). Concentration profiles during post-dilution (thin line) and mid-dilution (bold line) HDF for urea (A), creatinine (B) and uric acid (C). *P < 0.05 between post-dilution and mid-dilution HDF.
Conclusion

For middle molecules like β2M, mid-dilution HDF was previously found superior to post-dilution HDF. The present study showed that mid-dilution HDF is as efficient as post-dilution HDF for small water-soluble solutes and protein-bound solutes. Furthermore, mid-dilution HDF was experienced as a feasible dilution technique without problems of clotting, clogging and/or high transmembrane pressures.

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Conflict of interest statement. None declared.

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