Middle molecule elimination in expanded haemodialysis: only convective transport?

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ABSTRACT

Background. New high-retention onset dialysers have shown improved efficacy in the elimination of uraemic toxins, and their degradative capacity has been compared with high convective volumes of online haemodiafiltration. Haemodialysis (HD) using high-flux membranes leads to convective transport by internal filtration [direct filtration (DF)/backfiltration (BF)] and allows the removal of middle molecules (MMs). The aim of this study was to assess solute transport mechanisms in expanded HD (HDx).

Methods. In 14 4-h HDx sessions with Theranova-500 dialysers under similar dialysis conditions (blood flow 400 mL/min, dialysate flow 700 mL/min, dialysate temperature 35.5°C), pressures at the inlet and outlet of both dialyser compartments (P_{bi}, P_{bo}, P_{di} and P_{do}) were collected hourly to estimate DF/BF volumes by semi-empirical methods. Uraemic toxins with various molecular weights were measured pre-dialysis, at 1 h (pre-filter and post-filter) and post-dialysis to calculate molecules’ reduction over time and dialyser in vivo clearances.

Results. Ultrafiltration was 1.47 ± 0.9 L and Kt/V 1.74 ± 0.3. Hydrodynamic data (P_{bi}: 259 ± 39, P_{bo}: 155 ± 27, P_{di}: 271 ± 30, P_{do}: 145 ± 29 mmHg and oncotic pressure 22.0 ± 3.5 mmHg) allowed the estimation of DF/BF rates. DF flow ranged from 29.5 ± 4.2 to 31.3 ± 3.9 mL/min and BF flow ranged from 25.1 ± 2.3 to 23.4 ± 2.6 mL/min. The highest calculated DF volume was 7506.8 ± 935.3 mL/session. Diffusive clearances (K_d) of all solutes were higher than their convective transport (all P < 0.001) except for prolactin (23 kDa) clearances, which showed no differences. Total clearances of all solutes were correlated with their K_d (ρ = 0.899–0.987, all P < 0.001) and Kt/V correlated with all reduction rates (ρ = 0.661–0.941, P = 0.010 to < 0.001). DF flow was only associated with urea (ρ = −0.793, P = 0.001), creatinine (ρ = −0.675, P = 0.008) and myoglobin clearance (ρ = 0.653, P = 0.011).

Conclusion. Results suggest that diffusive transport is a main mechanism of MM elimination in HDx. HDx offers an efficient depuration of MM without the need for high convective volumes.

Keywords: backfiltration, expanded haemodialysis (HDx), high-retention onset (HRO), medium cut-off (MCO), middle molecules
INTRODUCTION

The elevated mortality rates of patients on haemodialysis (HD) have been related to the retention of a wide variety of uraemic toxins [1, 2]. Although small-sized (<500 Da) water-soluble solutes are easily removed by diffusive transport mechanisms, larger-sized molecules [i.e., middle molecules (MMs)] sized 500 Da to 60 kDa and protein-bound solutes are difficult to eliminate with conventional dialysis techniques [3]. However, the use of high-permeability membranes (high-flux HDx) allows MM elimination by internal filtration [direct filtration (DF)/backfiltration (BF)] [4].

The association of MMs with higher morbidity and mortality has boosted the development of convective therapies over recent years. Online haemodiafiltration (OL-HDF) with high convective volumes obtains better efficacy in MM elimination compared with high-flux HD, and it has been associated with improved outcomes [5, 6]. However, high-permeability dialysers used in high-flux HD and OL-HDF have cut-off values around 20 kDa [7], which limits the elimination of larger molecules through the membrane pores.

The development of medium cut-off or high-retention onset (HRO) dialysers has defined a new concept: expanded HD (HDx) [8]. Compared with high-flux membranes, the design of HRO membranes results in higher cut-off values, close to but lower than that of albumin, enabling the passing of larger solutes. Their tight pore size distribution results in a steep sieving coefficient (Sc) curve with molecular weight retention onset (MWRO) (where Sc ≈ 0.9) and molecular weight cut-off (MWCO) (where Sc ≈ 0.1) very close to each other, resulting in improved solute removal from a wide range of sizes by minimizing albumin leakage [9]. Other papers studying HDx have observed similar results of high convective volumes of OL-HDF in smaller MM removal, which are even higher for larger MMs [10, 11].

The aim of this study was to assess the transport mechanisms for uraemic toxin elimination in HDx with HRO membranes.

MATERIALS AND METHODS

Study design

A prospective observational analysis of HDx features was performed in 14 patients on maintenance OL-HDF. In a midweek dialysis session, patients underwent an HDx session with Theranova-500 (Baxter International Inc., Deerfield, IL, USA) under similar dialysis conditions: blood flow (Qb) 400 mL/min, dialysate flow (Qd) 700 mL/min, dialysate temperature 35.5°C and 240-min long. All sessions were carried out using a DDB-EXA dialysis monitor (Nikkiso Inc., Tokyo). Dialysate fluid composition and conductivity, system anticoagulation, and ultrafiltration pattern and volume were individualized according their usual dialysis prescription.

Inclusion criteria

Inclusion criteria were age > 18 years, habitual Qb > 400 mL/min and post-dilution OL-HDF as maintenance therapy. Exclusion criteria were vascular access issues, events or hospitalizations in the last 3 months and history of hypersensitivity reactions to synthetic HD membranes. Of the 34 patients from our dialysis unit who met all criteria, 14 patients were randomly selected for the study. The patients included signed informed consent forms and the study complies with the Declaration of Helsinki.

Laboratory

Plasmatic levels of small-sized uraemic toxins and MMs (urea: 60 Da, phosphate: 96 Da, creatinine: 113 Da, β2-microglobulin: 11.8 kDa, cystatin-C: 13 kDa, myoglobin: 17.2 kDa and prolactin: 23 kDa), and serum albumin levels (66 kDa), were assessed pre-dialysis, post-dialysis, and at 60 min at blood inlet (pre-filter) and outlet (post-filter) into the dialyser.

Dialyser excretion ratios (ER) and total dialyser clearances (Kt/V) of uraemic toxins and albumin were calculated from the blood compartment at 1 h. Also, solute reduction ratios (RRs) in the whole session, in the first hour and in the last 3 h were calculated to evaluate their elimination throughout the session, using the following formulas:

\[
Kt/V = \frac{\text{Qb} \times \text{ER}}{100}
\]

To calculate albumin RRs, albumin levels at 60 and 240 min ([albumin]post) were corrected with ultrafiltration in the whole session, in the last 3 h or in the first hour according to the corresponding period [12]:

\[
\text{RR} = \frac{\text{[Albumin]post} - \text{[Albumin]predialysis}}{\text{[Albumin]predialysis} - \text{[Albumin]predialysis}}
\]

Blood viscosity parameters [haemoglobin, haematocrit (HTC), total proteins (Ct), albumin and gammaglobulins] were evaluated at the beginning and at 60 min to calculate oncotic pressure [13] (o) and plasma and blood viscosity [14] (μ) with the formulas:

\[
\pi = 2.1 \cdot C_T + 0.16 \cdot (C_P)^2 + 0.009 \cdot (C_P)^3
\]

\[
\mu = 0.6915 \cdot \left( \frac{(1 - 2.22 \cdot C_P)}{7} \right) \cdot (1 + 2.5 \cdot \frac{\text{HTC}}{100})
\]

Monitor screen parameters

By using different pressure sensors, we collected arterial pressure (AP), blood pressure at the inlet (Pdi) and outlet of the dialyser (Pdo), dialysate pressure at the inlet (Pdii) and outlet (Pdoi), and transmembrane pressure (TMPm) each hour. Every hour, the average TMP (TMPa) was calculated using inlet and outlet pressures [TMP = (Pdii + Pdoi) – (Pdi + Pdo)]. Also, the inlet TMP [TMPi = (Pdi – Pdii)] and pressure drop in both compartments were obtained hourly.

Other monitor screen data included Qb, Qd ultrafiltration, urea clearance by ultraviolet light absorbance (Kt/VDA) (Dialysis Dose Monitor, Nikkiso), urea RR (URR DA) and KT/V (Kt/V DA). Kt/V DA was obtained with Kt/VDA and urea distribution volume (UDV) by pre-dialysis bioimpedance, using the Daugirdas formula for spKt/V [15].

Convective volumes calculation

Convective transport was estimated using different semi-empirical models previously used to quantify internal filtration.
with Theranova [16]. Models were developed using $P_{bi}$, $P_{bo}$, $P_{di}$, $P_{do}$ and dialyser characteristics provided by the manufacturer (ultrafiltration coefficient, $K_{u} = 59 \text{mL/h/mmHg}$; surface area: 2 m$^2$). The area under the TMP curve (AUC$_{TMP}$) on the axial axis of the dialyser represents DF/BF flow. DF flow (Q$_{DF}$) was obtained from the area where DF occurs (A$_{DF}$) and from the average TMP in that DF area, and BF flow (Q$_{BF}$) was obtained from the BF area (A$_{BF}$) and from the average TMP in that BF area:

$$Q_{DF} = K_{DF} \cdot A_{DF} \cdot \text{TMP}_{DF}$$

$$Q_{BF} = K_{BF} \cdot A_{BF} \cdot \text{TMP}_{BF}$$

The first ‘linear’ model (Model A1) was obtained assuming a linear pressure drop in both compartments and therefore a linear profile of TMP along the dialyser. The cut-off point ($X_0$) between the lines describing pressures in both compartments reflects the section of the dialyser where ultrafiltration flow changes from DF to BF, and was calculated with the formula:

$$X_0 (A1) = \frac{P_{do} - P_{bi}}{(P_{bo} - P_{bi}) - (P_{di} - P_{do})} = \frac{\text{TMP}_{d} \cdot \Delta P_{b} + \Delta P_{d}}{}$$

In another version of the linear model (Model A2), blood oncotic pressure ($\pi$) was added to the previous formula:

$$X_0 (A2) = \frac{P_{do} - (P_{bo} - \pi) - (P_{di} - P_{do})}{((P_{bo} - \pi) - (P_{di} - \pi)) - (P_{di} - P_{do})} = \frac{\text{TMP}_{d} - \pi}{\Delta P_{b} + \Delta P_{d}}$$

The second ‘geometric’ model (Model B1) also assumes linear pressure drops in both compartments, but with different slopes for the line that characterizes the DF and BF segments. This model assumes that, in the absence of ultrafiltration, AUC$_{TMP}$ for DF and AUC$_{TMP}$ for BF must be equal to ensure volumetric control; in case of ultrafiltration, AUC$_{TMP}$ for BF must be greater than AUC$_{TMP}$ for BF, and it is equivalent to the sum of AUC$_{TMP}$ for BF and the TMP needed to achieve the programmed ultrafiltration (TMP$_{df}$) ($Q_{df} = Q_{df} + Q_{uf}$). The cut-off point ($X_0$) between pressure lines was calculated with the formula:

$$\frac{\text{TMP} \cdot X_0}{2} = \frac{\text{TMP}_{b} \cdot (1 - X_0)}{2} + \text{TMP}_{df}$$

So:

$$X_0 \ (B1) = \frac{\text{TMP}_{b} \cdot (1 - X_0)}{2}$$

In another version of the geometric model (Model B2), $\pi$ was added to the previous formula:

$$X_0 \ (B2) = \frac{\text{TMP}_{b} + \pi + (2 \cdot \text{TMP}_{df})}{\text{TMP}_{b} + \text{TMP}_{df}}$$

Models A2 and B2 consider the effect of oncotic pressure on convective transport, so it was subtracted from TMP$_{df}$ to calculate Q$_{uf}$ and it was added to TMP$_{bf}$ to calculate Q$_{bf}$. Both models understand oncotic pressure as a constant value along the dialyser and throughout the session. Pre-dialysis oncotic pressure was used to estimate overall DF/BF volumes in the whole session, and oncotic pressure at 60 min to estimate DF/BF flows in the first hour.

**Efficacy measurements: transport mechanisms for molecule elimination**

Convective clearances ($K_{c}$) were calculated with DF flow at 60 min and theoretical $S_{c}$ ($K_{c} = Q_{df} \cdot S_{c}$). According to membrane characteristics (MWRO $\approx 12$ kDa and MWCO $\approx 50$ kDa) [9], and assuming a linear reduction of $S_{c}$ as the molecular weight increases, theoretical $S_{c}$ values obtained for MMs were: $S_{c}$ beta2-microglobulin 0.90; $S_{c}$ cystatin-C 0.88; $S_{c}$ myoglobin 0.79; and $S_{c}$ prolactin 0.67. An $S_{c} = 0.01$ was used for albumin and $S_{c} = 1$ was used for low-molecular weight solutes. Diffusive clearances ($K_{d}$) at 60 min were estimated with the difference between $K_{o}$ and convective clearances at that time ($K_{s} = K_{o} - K_{c}$).

Overall, mass transfer (MT$_{ovr}$) was estimated from $K_{o}$ using the formula:

$$\text{MT}_{ovr} = K_{o} \cdot \frac{(|\text{Solute}|_\text{pre} - |\text{Solute}|_\text{post})}{\ln (\text{|Solute|}_\text{pre}/\text{|Solute|}_\text{post})} \cdot \text{Time}$$

Overall clearances ($K_{ovr}$) were calculated from MT$_{ovr}$ and the AUC of plasmatic levels, with the formula [17]:

$$K_{ovr} = \frac{\text{MT}_{ovr}}{\text{AUC}}$$

$$\text{AUC} = \left(\frac{|\text{Solute}|_\text{pre} + |\text{Solute}|_\text{post}}{2}\right) \frac{60}{240} + \left(\frac{|\text{Solute}|_\text{post}}{2}\right) \frac{180}{240}$$

Overall convective clearances ($K_{ovr|0} = K_{ovr|0}$) were estimated from average DF flow and theoretical $S_{c}$. Overall diffusive clearances ($K_{ovr|0}$) were calculated with the difference between $K_{ovr}$ and $K_{ovr|0}$ [$K_{ovr|0} = K_{ovr} - K_{ovr|0}$].

**Statistical analysis**

Statistical analysis was performed using SPSS Statistics, version 21 (SPSS, Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to analyse the variables’ distribution patterns. Descriptive results were expressed as mean $\pm$ standard deviation for normally distributed values, median (interquartile range) for non-normal distributed quantitative variables and percentages for qualitative variables. Given the small sample size, non-parametric tests (Spearman, Wilcoxon and Mann–Whitney) were used to analyse the association between efficacy variables, convective transport, patient features and molecule elimination. A value of $P < 0.05$ was considered statistically significant with a 95% confidence interval.

**RESULTS**

**Patients’ features**

Demographic data, patient dialysis-related features, anthropometric measurements and body composition are shown in Table 1.

**Dialysis features**

Average effective $Q_{b}$ was $401.4 \pm 3.1$ mL/min, with blood pump $Q_{b} 428.3 \pm 20.6$ mL/min and AP $103.5 \pm 42.5$ mmHg. Pre-dialysis weight was $68.5 \pm 18.9$ kg and ultrafiltration volume was
Table 1. Patient features

| Patient feature               | Mean ± SD* Percentage; n^b |
|------------------------------|-----------------------------|
| Age (years)                  | 64.6 ± 17.6                 |
| Gender; male (%; n)          | 71.4; 10                    |
| CKD aetiology (%; n)         |                             |
| Diabetes                     | 21.4; 3                     |
| Glomerular                   | 14.3; 2                     |
| Vascular                     | 14.3; 2                     |
| PKD                          | 14.3; 2                     |
| Interstitial                 | 7.1; 1                      |
| Other/unknown                | 28.6; 4                     |
| Previous kidney transplant   | 7.1; 1                      |
| Dialysis vintage (months)    | 49.6 ± 36.2                 |
| Residual diuresis volume     | > 500 mL/day (%; n)         | 35.7; 5 |
| Vascular access              |                             |
| AVF                          | 78.6; 11                    |
| AVG                          | 7.1; 1                      |
| CVC                          | 14.3; 2                     |

Anthropometric measurements and body composition

- Pre-dialysis weight (kg): 68.5 ± 18.9
- Post-dialysis weight (kg): 67.0 ± 19.2
- BMI (kg/m^2): 22.8 ± 4.93
- BSA (m^2)^c: 1.77 ± 0.26
- UDV (L): 37.8 ± 11.7

^aQuantitative variables are expressed as mean and SD.
^bQualitative variables are expressed as percentages and absolute values.
^cBSA using DuBois and DuBois formula.
^dData from pre-dialysis bioimpedance spectroscopy.

1.47 ± 0.89 L. Table 2 shows dialysis parameters obtained hourly from the monitor screen.

Convective transport

Figure 1 describes blood and dialysate pressures, TMP profiles along the axial axis and estimated convective volumes obtained from each semi-empirical model. The highest DF estimated rates were 1876.7 ± 233.8 mL/h and 1717.9 ± 218.4 mL/h with geometric Models B1 and B2, respectively.

Pre-dialysis blood tests showed haemoglobin 11.1 ± 3.3 g/dL, HCT 32.7 ± 4.3% and total proteins 6.31 ± 0.67 g/dL (albumin 3.78 ± 0.43; gammaglobulins 1.14 ± 0.38). Pre-dialysis blood oncoptic pressure was 22.0 ± 3.5 mmHg and blood viscosity was 1.51 ± 0.1 cP. Oncoptic pressure at 60 min was 20.7 ± 3.4 mmHg.

Higher haemoglobin levels were associated with greater estimated convective transport in all models (DF volume: \( \rho = 0.609-0.825 \), P = 0.023 to <0.001; BF volume: \( \rho = 0.561-0.759 \), P = 0.003–0.002), related to higher TMP (\( \rho = 0.829, P < 0.001 \)) and TMP (\( \rho = 0.535, P = 0.049 \)). Total proteins were only associated with higher DF volume in Model A1 (\( \rho = 0.548, P = 0.042 \)) and higher BF volume in Model A2 (\( \rho = 0.542, P = 0.045 \)) and Model B1 (\( \rho = 0.559, P = 0.038 \)). No association was observed between albumin or gammaglobulins and DF/BF volumes.

Efficacy in molecule elimination

Plasmatic levels of uraemic toxins and albumin, and their RRs throughout the session, are summarized in Table 3, whereas clearances and mass transfers of each solute are included in Table 4.

**DISCUSSION**

The present analysis of the mechanisms for uraemic toxin elimination with HRO membranes suggests that diffusion plays an essential role in the removal of a wide variety of molecules up to 23 000 Da. The use of these HRO membranes could change the widespread concept that diffusion is only useful for the elimination of small solutes [18, 19]. Therefore, high convective volumes are not necessary to achieve effective removal of MMs. In most situations where there are limitations regarding achieving efficient convective transport, patients could benefit from the prescription of HDx.

Results in molecule elimination were similar to those found in other recent studies [10, 20] and comparable to those achieved in post-dilution OL-HDF. As seen in Figure 2, the Kt of all molecules exceeded their Kd. Discarding the convective component of total clearance and assuming the absence of molecule...
adsorption to the membrane, it can be deduced that diffusive transport mechanisms play a major role in the elimination of these solutes.

Convective transport

Numerous studies have attempted to quantify convective transport by internal filtration inside the dialyser by several different methods [21, 22]. Semi-empirical models included multiple errors in the estimation of DF/BF flows while linear models overestimated BF rates, which is not compatible with multiple errors in the estimation of DF/BF flows while linear models have estimated DF/BF rates of

Diffusive transport

The development of these 'high pore size' membranes has probably led to a wider range of molecules that can be efficiently eliminated by diffusion. As shown in Tables 3 and 4, solute removal decreases as their size increases, both their elimination in the dialyser (ER and \(K_d\)) and globally throughout the session (\(R_R\) and \(MT_{ov}\)). It should be noted that this 'size-dependent' decrease in solute clearance is proportionally much greater than the decrease in \(S_i\) and, therefore, cannot be explained solely by the reduction in \(K_d\). However, the reduction in \(K_d\) with the increase in molecular size is proportionally more consistent with and parallel to the reduction in \(K_D\) (Figure 2). The reduction in diffusive transport is probably conditioned by a decreasing mobility of larger solutes as their size increase.

For molecules over 20 kDa (such as prolactin), the contribution of \(K_d\) is reduced to be comparable with \(K_D\), which determines an equitable contribution of both transport mechanisms in their elimination. Nevertheless, this progressive reduction in \(K_d\) with the increase in size conditions the expected diffusion of molecules >25-30 kDa to be minimal or negligible, while convective transport becomes more important. The lack of information for molecules greater in size than prolactin is a major limitation of the study, since they have been shown to be effectively eliminated with HDx. Further studies are required to

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**Table 2. Dialysis parameters obtained from monitor screen**

| Dialysis parameter | 5 min | 60 min | 120 min | 180 min | 240 min |
|--------------------|-------|--------|---------|---------|---------|
| Effective \(Q_{ef}\) (mL/min) | 400.9 ± 3.8 | 400.7 ± 4.6 | 401.9 ± 2.8 | 401.9 ± 3.1 | 401.4 ± 3.5 |
| Ultrafiltration (L) | – | 0.38 ± 0.23 | 0.74 ± 0.45 | 1.11 ± 0.69 | 1.47 ± 0.89 |
| \(K_{abs} DDM\) (mL/min) | – | 337.7 ± 61.5 \(^{a,b}\) | 303.1 ± 51.2 \(^{a,b}\) | 286.9 ± 51.1 \(^{a,c}\) | 275.7 ± 51.7 \(^{a,c}\) |
| \(K_t/V\) | – | 0.55 ± 0.13 | 0.96 ± 0.19 | 1.39 ± 0.26 | 1.74 ± 0.32 |
| URR (%) | – | 40.4 ± 7.4 | 58.1 ± 7.3 | 70 ± 7 | 76.9 ± 6 |
| \(P_0\) (mmHg) | 255 ± 36 | 260 ± 43 | 260 ± 40 | 261 ± 42 | 260 ± 44 |
| \(P_i\) (mmHg) | 155 ± 27 | 161 ± 32 | 153 ± 29 | 154 ± 30 | 153 ± 29 |
| \(P_o\) (mmHg) | 271 ± 34 | 276 ± 34 | 271 ± 31 | 269 ± 32 | 269 ± 32 |
| \(P_{ol}\) (mmHg) | 144 ± 27 | 150 ± 35 | 144 ± 31 | 143 ± 32 | 144 ± 32 |
| 
| \(TMP_m\) (mmHg) | 1.6 ± 2.4 | 1.4 ± 5.1 | 1.9 ± 4.5 | 1.6 ± 5 | 2.6 ± 5.6 |
| \(TMP_c\) (mmHg) | 2.8 ± 7.8 | -2.1 ± 8.7 | -1 ± 7.7 | 1 ± 7.9 | -0.4 ± 9.4 |
| \(TMP_{ul}\) (mmHg) | 110.4 ± 17.6 | 110.5 ± 17.2 | 115.9 ± 15.4 | 117.5 ± 17.7 | 115.8 ± 18.9 |
| \(TMP_{ol}\) (mmHg) | -115.9 ± 12.8 | -114.6 ± 4.8 | -118 ± 6.1 | -115.4 ± 4.9 | -116.6 ± 5.1 |
| \(dP_{0}\) (mmHg) | 99.7 ± 19\(^a\) | 99.3 ± 19.2 | 106.4 ± 17.7 | 106.5 ± 20.3 | 106.9 ± 20.6\(^*\) |
| \(dP_{d}\) (mmHg) | 126.6 ± 12.1 | 125.8 ± 1.8 | 127.5 ± 2.2 | 126.4 ± 1.8 | 125.6 ± 2.9 |

\(^a\) Wilcoxon test for paired samples (\(P=0.003\)).
\(^b\) Wilcoxon test for paired samples (\(P=0.001\)).
\(^c\) Wilcoxon test for paired samples (\(P=0.002\)).
\(^d\) Wilcoxon test for paired samples (\(P=0.001\)).
\(^*\) Wilcoxon test for paired samples (\(P=0.026\)).

\(a-e\) characters represent comparisons between 60 and 120 min (a), between 120 and 180 min (b), between 180 and 240 min (c), between 60 and 240 min (d), and between 5 and 240 min (e).

DDM: dialysis dose monitor; \(dP_{0}\): pressure drop in the dialysate compartment; \(dP_{d}\): pressure drop in the dialysate compartment; \(K_{abs}\): urea clearance measured by UV absorbance; \(K_t/V\): spKt/V by Daugirdas, from urea clearance measured by UV absorbance and urea distribution volume measured by bioimpedance; \(P_0\): pressure at the inlet of blood compartment; \(P_{ol}\): pressure at the outlet of dialysate compartment; \(P_{ol}\): pressure at the outlet of dialysate compartment; \(Q_{ef}\): blood flow; \(TMP_m\): transmembrane pressure from monitor screen; \(TMP_c\): calculated 4-points transmembrane pressure; \(TMP_{ul}\): transmembrane pressure at blood inlet; \(TMP_{ol}\): transmembrane pressure at blood outlet; URR: urea reduction ratio measured by UV absorbance.

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**Note:**

The table shows key dialysis parameters obtained from the monitor screen, including effective ultrafiltration rate (Q_{ef}), ultrafiltration (L), K_{abs} DDM, K_t/V, and URR. The data are presented for different time points: 5 min, 60 min, 120 min, 180 min, and 240 min. The table includes statistical comparisons between these parameters using Wilcoxon tests for paired samples.

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**Figure 1:**

This figure illustrates the convective transport mechanism in dialysis. The image shows the flow of blood through the dialyser, highlighting the effect of convection on solute removal. It includes a representation of the membrane's permeability and the direction of solute movement.

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**Figure 2:**

This figure depicts the diffusive transport mechanism in dialysis. It highlights the role of diffusion in solute clearance, emphasizing the importance of size-dependent clearance in different solutes. The figure includes a graph showing the reduction in diffusive transport as a function of solute size.
evaluate solute transport mechanisms for those large-sized MMs with HDx.

Similar to the interaction mechanisms between diffusion and convection described with other techniques [26], a negative correlation was found between the diffusion of small solutes (urea and creatinine) and convective transport. In contrast, the association of myoglobin clearance, both with its $K_d$ and with DF flow, suggests that both mechanisms are complementary for the elimination of MMs rather than competitive.

While blood viscosity data influenced convective transport volumes, they had no association with molecules elimination, which is probably explained by the predominant role of diffusion in their removal. On the other hand, the association of $K_t/V$ with small-sized solutes and MM (at least up to 23 kDa)
Table 4. Uraemic toxin ERs, clearances at 60 min, mass transfer and overall clearances

| Solute         | ER (%) | $K_D$ (mL/min) | $K_C$ (mL/min) | $K_{ovr}$ (mL/min) | MT$_{ovr}$ (mg) | $K_{ovr(c)}$ (mL/min) | $K_{ovr(d)}$ (mL/min) |
|----------------|--------|---------------|---------------|-------------------|-----------------|----------------------|----------------------|
| Urea           | 84.9 ± 1.9 | 341.8 ± 7.2  | 30.6 ± 3.7    | 311.2 ± 9.6       | 40.2 ± 11.1 (10$^5$) | 357.8 ± 34.3          | 31.3 ± 3.9          | 326.5 ± 34.9         |
| Phosphate      | 75.4 ± 6.8 | 304.1 ± 27.5  | 30.6 ± 3.7    | 273.5 ± 27.2      | 1918 ± 463      | 375.9 ± 37.9          | 31.3 ± 3.9          | 344.6 ± 38.4         |
| Creatinine     | 68.8 ± 3.8 | 278.3 ± 15.8  | 30.6 ± 3.7    | 247.7 ± 18.2      | 2488 ± 965      | 307.2 ± 27.0          | 31.3 ± 3.9          | 275.9 ± 28.9         |
| β2-microglobulin | 35.9 ± 3.6 | 147.9 ± 13.9  | 27.7 ± 3.3    | 120.2 ± 13.2      | 359 ± 126       | 175.5 ± 21.0          | 28.3 ± 3.5          | 147.2 ± 20.4         |
| Cystatin C     | 31.1 ± 2.1 | 129.4 ± 8.5   | 26.9 ± 3.3    | 102.5 ± 7.8       | 103 ± 20        | 156.3 ± 11.4          | 27.5 ± 3.4          | 128.9 ± 11.3         |
| Myoglobin      | 18.2 ± 2.8 | 78.1 ± 11.3   | 24.2 ± 2.9    | 53.9 ± 10.1       | 2399 ± 1228$^\text{a}$ | 92.1 ± 14.9          | 24.7 ± 3.1          | 67.4 ± 13.8          |
| Prolactin      | 10.1 ± 8.0 | 46.1 ± 30.8   | 20.4 ± 2.5    | 25.7 ± 31.0       | 113 ± 93 (10$^{-3}$) | 52.3 ± 34.9          | 20.9 ± 2.6          | 31.4 ± 35.2          |
| Albumin        | -0.77 ± 4.05 | -9.4 ± 17.1   | -               | -                | -              | -9.5 ± 17.9          | -                   | -                   |

ER by dialyser at 60 min; $K_D$ at 1 h measured from blood compartment; $K_C$ and $K_{ovr}$ were calculated with the highest DF flow observed (Model B1) using theoretical sieving coefficients ($S_c = 0.90$ for β2-microglobulin, $S_c = 0.88$ for cystatin C, $S_c = 0.79$ for myoglobin, $S_c = 0.67$ for prolactin, $S_c = 0.01$ for albumin, and $S_c = 1$ for urea, creatinine and phosphate).

**FIGURE 2:** Total, convective and diffusive clearances. (A) Measurements at 60 min; (B) overall clearances.
elimination could also reflect the importance of diffusive transport. As Kt/V continues to be the reference for dialysis dose standardization [27, 28], this adds the possibility of using Kt/V as a non-invasive, adjusted to patient, on-line/real-time method for monitoring the efficacy of HDx in the removal not only of small solutes, but also of MM.

Adsorption

Results were obtained assuming the absence of absorption to the membrane. However, the exposure of blood to the membrane surface results in significant protein adsorption, which can have a significant impact on solute removal [29]. Given the progressive reduction of both diffusive and convective mechanisms as molecule sizes increase (due to slower motion of the solutes and a reduction in membrane S, respectively), adsorption may have greater relative importance regarding larger molecules. Although hard to measure in a clinical setting, other studies comparing clearances calculated from the blood compartment with clearances obtained from dialysates could estimate roughly adsorptive mechanisms with these membranes.

Applicability

The main advantage of HRO membranes is the possibility of performing HDx with classic conventional HD systems, providing similar or even superior depurative capacity to high convective volumes obtained with high-flux membranes, without the need for replacement systems or solutions. Most situations in which efficient convective transport cannot be achieved (limitations in Qb, haemoconcentration, etc.) could probably benefit from the prescription of HDx with HRO membranes to obtain appropriate uremic toxin depuration, but more studies are necessary to evaluate the clinical benefits of HDx.

A relevant issue to be clarified about estimated convective transport, which seems to be similar to that found in other techniques such as high-flux HD or low-efficiency convective therapies [30], is whether HRO membranes can be used when dialysis water conditions needed for high-flux HD are met but not for OL-HDF. Nevertheless, given the results, it should be remembered that endotoxin (lipopolysaccharides, 5227 Da) or other dialysate solutes could be transferred to the patient, not only by convective transport with BF, but also by diffusion through the membrane.

CONCLUSION

The results presented suggest that diffusive transport is a main mechanism of MM elimination in HDx. HDx offers efficient depuration of MMMs without the need for high convective volumes, so it could benefit patients in which the ability to attain an effective convective dose is limited.

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AUTHORS’ CONTRIBUTIONS

N.M. participated in the conception and the design of the study, in the collection, analysis and interpretation of data, and have written the original manuscript. A.S., E.T. and A.M.G.P. contributed in the collection of the data. A.V., S.A., I.A., A.M.G.F., A.S. and J.L. contributed in the analysis and interpretation of data, and provided intellectual content of critical importance. A.V., S.A. and J.L. revised the article and approved the final version to be published.

CONFLICT OF INTEREST STATEMENT

None declared.

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