Alterations of peritoneal transport characteristics in dialysis patients with ultrafiltration failure: tissue and capillary components

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ABSTRACT

Background. Ultrafiltration failure (UFF) in peritoneal dialysis (PD) patients is due to altered peritoneal transport properties leading to reduced capacity to remove excess water. Here, with the aim to establish the role of local alterations of the two major transport barriers, peritoneal tissue and capillary wall, we investigate changes in overall peritoneal transport characteristics in UFF patients in relation to corresponding local alterations of peritoneal tissue and capillary wall transport properties.

Methods. Six-hour dwell studies using 3.86% glucose solutions and radioisotopically labelled serum albumin added to dialysate as a volume marker were analysed in 31 continuous ambulatory PD patients, 20 with normal ultrafiltration (NUF) and 11 with UFF. For each patient, the physiologically based parameters were evaluated for both transport barriers using the spatially distributed approach based on the individual intraperitoneal profiles of volume and concentrations of glucose, sodium, urea and creatinine.

Results. UFF patients as compared with NUF patients had increased solute diffusivity in both barriers, peritoneal tissue and capillary wall, decreased tissue hydraulic conductivity and increased local lymphatic absorption and functional decrease in the fraction of the ultra-small pores. This resulted in altered distribution of fluid and solutes in the peritoneal tissue, and decreased penetration depths of fluid and solutes into the tissue in UFF patients.

Conclusions. Mathematical modelling using a spatially distributed approach for the description of clinical data suggests that alterations both in the capillary wall and in the tissue barrier contribute to UFF through their effect on transport and distribution of solutes and fluid within the tissue.

Keywords: blood capillary wall, peritoneal tissue, peritoneal transport, ultrafiltration failure

INTRODUCTION

Ultrafiltration failure (UFF) is a serious complication of peritoneal dialysis (PD) that may lead to technique failure and transfer to haemodialysis. Although UFF may occur at any stage during the course of PD therapy, the probability of developing UFF increases with time on treatment, and its prevalence may exceed 30% in long-term PD patients [1, 2]. UFF is characterized by reduced peritoneal fluid transport capacity, typically defined as UF <400 mL after 4-h dwell with 3.86% glucose, leading to insufficient fluid removal, and possible signs of fluid overload [3]. It is important to distinguish UFF from other causes of inadequate fluid removal such as impaired fluid outflow through the catheter due to its obstruction, subcutaneous leakage, excessive fluid intake and loss of residual renal function [4, 5].

Insufficient fluid removal is a consequence of long-term PD and especially exposure to hypertonic glucose solutions, leading to progressive alterations of the peritoneal transport system (PTS), typically called peritoneal membrane. This complex transport system consists of capillaries, lymphatic vessels, interstitium and parenchymal cells in the peritoneum and in tissues surrounding the peritoneal cavity. So far, four types of UFF have been described and related to different pathophysiological changes of PTS: (i) high diffusive permeability of peritoneal membrane, often related to a large effective peritoneal surface area; (ii) low osmotic conductance to glucose; (iii) low diffusive permeability for solutes, often related to a reduced effective peritoneal surface area, caused by fibrosis, vasculopathy and sclerosis of peritoneal membrane; and (iv) high peritoneal absorption rate [2, 5].

Typically, theoretical approaches, such as the membrane model and the three-pore model (3PM), are applied using clinical data from patients with UFF, allowing quantitative estimation of PTS properties and detection of possible reasons leading

Table 1. Characteristics of patients with NUF and UFF

Patients characteristics	NUF group	UFF group
Number of patients	20	11
Sex	9 females, 11 males	6 females, 5 males
Age, years	55.6 ± 11.7 (M: 59; R: 36–74)	60.3 ± 11.5 (M: 65; R: 36–71)
Body weight, kg	64.6 ± 11.6	69.8 ± 5.8
Height, cm	171.3 ± 9.1	166.4 ± 7.4
Mean time on PD, months	18 ± 17 (M: 11; R: 1–58)*	33 ± 21 (M: 26; R: 1–72)

Number of patients, sex, age, body weight (before session), height, mean time on PD, presented as mean ± SD, with median (M) and range (R) when needed.

*P < 0.05 UFF versus NUF group.

to the observed alterations [1, 2, 4, 6, 7]. These phenomenological approaches are based on the concept of PTS as an aggregate entity, which however does not allow for the separation between tissue and capillary wall components of the barrier. In this study, in addition to the aggregated transport properties of PTS, we aimed at estimating transport properties of each of the two barriers components separately based on dwell studies in the peritoneal cavity.

The aim of the present study was to assess the alterations in the transport properties of the two major peritoneal transport barriers—tissue and capillary wall—in UFF patients and to apply obtained results to explain the local, functional reasons for UFF. In addition, we investigated how these changes associate with fluid and solutes penetration and distribution within the peritoneal tissue and with the overall peritoneal transport characteristics, as typically measured by others using a membrane approach.

MATERIALS AND METHODS

Thirty-one continuous ambulatory peritoneal dialysis (CAPD) patients underwent 6-h dialysis exchange using 2 L of dialysis fluid with 3.86% glucose (Dianeal, Baxter) according to a protocol described earlier [2, 8, 9]. Briefly, radioisotopically labelled serum albumin (RISA) was added to the dialysis fluid as a volume marker. Dialysate samples of 15 mL were taken initially (from the bag before infusion) and at 3, 15, 30, 60, 90, 120, 180, 240 and 360 min after the complete infusion of the dialysis fluid. Blood samples were taken before and at 180 and 360 min after the complete infusion of the dialysis fluid. Concentration of glucose, sodium, urea, creatinine and RISA was measured, see [9] for more details. The patients were divided into two groups: 20 patients having no clinical problems with UF capacity were selected as a control group [normal UF group, normal ultrafiltration (NUF)], whereas the remaining 11 patients were included in the UFF group (see Table 1 for detailed characteristics of both groups). None of the patients had peritonitis for at least 2 months before the session. UFF was defined clinically as: oedema and inability to reach ‘dry weight’ despite three or more exchanges per day with 3.86% glucose solution, and under restricted fluid intake, with duration of symptoms of overhydration exceeding 1 month, and no established cause of UFF such as peritonitis, dialysis leakage or catheter malfunction, see [2, 8] for more details. In this clinical study, performed before the International Society for Peritoneal Dialysis (ISPD) definition was introduced, 10 patients had net UF of <400 mL after 4 h,

while one patient was classified as UFF although net UF was 530 mL after 4 h with 3.86% glucose dialysis fluid, because the other of the above-mentioned criteria were present. Based on the classical membrane approach, 8 out of the 11 patients from the UFF group were classified as having high diffusive permeability rate for small solutes and normal peritoneal absorption rate (patients with high diffusive permeability rate, HDR group), whereas the remaining 3 patients had high (>4 mL/min) fluid absorption rate, defined based on elimination rate of RISA from the peritoneal cavity while having normal diffusive permeability (patients with high absorption rate, HAR group) [7, 10]. The patient who did not meet ISPD criteria was classified into the HDR group and, as we found in the current study, his local transport characteristics of both the barriers were similar to other patients from this group. The removal of this patient from analysis would not change the conclusions, and therefore we present results obtained for all UFF patients.

In order to estimate individual characteristics of PTS, the distributed approach was applied as described previously [11]. The intraperitoneal volume was estimated from the elimination rate of RISA and corrected for the infused and the samples volumes. Moreover, the appropriate corrections for concentration of solutes were applied as described in [12]. Fluid absorption rate from the peritoneal cavity was calculated from the elimination rate of RISA from the peritoneal cavity and compared with the value estimated from the model. In addition, based on the clinical data variability of the effective peritoneal surface, area (surface of tissue that surrounds peritoneal cavity and remains in the contact with dialysate), A , was taken into account (assuming $A = 260 \cdot V^{0.4}$, where V denotes intraperitoneal volume [13, 14]). Moreover, variability of intraperitoneal pressure caused by the changes of intraperitoneal volume was described based on the clinical data for drainage, infusion and dwell time as follows: $P = 0.008514 \cdot V$ for $V \leq 1000$ and $P = V/490 + 6.4733$ mmHg for $V > 1000$ mL [15–17].

Twelve patient-specific transport parameters were estimated based on the clinical data: (i) parameters of the capillary barrier: hydraulic conductance ($capHC$), the fractional input of ultra-small pores to the hydraulic conductance (α_{UP}); (ii) parameters of the tissue barrier: hydraulic conductivity ($tisHC$), reflection coefficient ($tisRef$, retardation factor for solute transport in the tissue), solutes diffusivity ($tisDif$, for each solute, separately) and lymphatic absorption; and (iii) other parameters: peritoneal absorption rate, residual volume. Transport parameters, such as reflection coefficient for solutes ($capRef$) and permeability across capillary wall ($capPS$), and osmotic conductance for

FIGURE 1: Mean values of individual clinical data and numerical simulations of the intraperitoneal fluid volume (V_D) and intraperitoneal concentration of glucose ($C_{D,G}$), sodium ($C_{D,Na}$), urea ($C_{D,U}$) and creatinine ($C_{D,Cr}$) as a function of dwell time for NUF and UFF groups.

glucose (*capOsmCond*), were calculated from the estimated values based on the 3PM of the capillary wall. In order to increase the accuracy of the description, the sodium permeability of the capillary wall was individually estimated for patients instead of using the values calculated from the 3PM of the capillary wall. The small- and large-pore sizes were assumed to be 46.7 and 245 Å, respectively, and the fractional input of large pores to the overall *capHC* was taken as 0.08. In addition, the functional relation between interstitial pressure and tissue hydration was assumed based on animal experiments as in other studies [11, 18, 19].

The local transport parameters that translate into the overall peritoneal membrane parameters were approximated as described in [20–22]. The final penetration depths of fluid and solutes (indicating the thickness of peritoneal tissue layer influenced by PD exchange) as well as the hydraulic conductance (*peritHC*) and diffusive transport parameters (*peritPS*) for the whole peritoneal membrane were calculated for hydrated interstitium and not for vasodilation, that is, for the conditions at the end of the peritoneal dwell by assuming the effective surface

area in contact with dialysate to be equal to 6000 cm² [22]. The glucose reflection coefficient (*peritRef*) and osmotic conductance (*peritOsmCond*) of the peritoneal membrane were approximated by taking into account the impact of ultrafiltration on the solute transport, that is, for the conditions during the initial phase of the peritoneal dwell.

The results were expressed as mean $\pm$ SD. The Mann-Whitney test was used for the comparison of two samples with the correction for the small sample size lower than 20, and non-parametric Spearman correlation coefficient between parameters was calculated whenever appropriate. Statistical significance was accepted if $P < 0.05$.

RESULTS

The mean intraperitoneal fluid volume and solutes concentration profiles during the dwell time for NUF and UFF patients, both clinically observed and model predicted, are shown in Figure 1; the minimized relative error was $<5\%$ in both groups. Significant differences, in properties of the transport through

Table 2. Estimated transport parameters for the interstitium and capillary wall (mean $\pm$ SD) of patients with NUF ($n = 20$), UFF ($n = 11$), subdivided into HDR ($n = 8$) and HAR ($n = 3$) group

Parameter	NUF group ($n = 20$)	UFF group ($n = 11$)	UFF HDR group ($n = 8$)	UFF HAR group ($n = 3$)	Units
Interstitial transport					
<i>tisHC</i> · 10 ⁶	2.8 $\pm$ 2.4	1.2 $\pm$ 0.5*	1.1 $\pm$ 0.3**	1.6 $\pm$ 0.5	cm ² /(min·mmHg)
<i>tisRef</i> · 10 ³	3.5 $\pm$ 2.6	2.1 $\pm$ 2.6	2.3 $\pm$ 3.1	1.8 $\pm$ 0.8	
Tissue lymphatic absorption · 10 ⁴	2.9 $\pm$ 1.3	4.6 $\pm$ 1.2*	4.9 $\pm$ 1.1**	3.6 $\pm$ 0.7	1/min
<i>tisDiff</i> · 10 ⁴ for:					
Glucose	0.60 $\pm$ 0.13	0.80 $\pm$ 0.21*	0.78 $\pm$ 0.23**	0.86 $\pm$ 0.19***	cm ² /min
Sodium	0.28 $\pm$ 0.12	0.32 $\pm$ 0.24	0.33 $\pm$ 0.27	0.29 $\pm$ 0.16	cm ² /min
Urea	2.14 $\pm$ 0.86	2.11 $\pm$ 0.99	2.15 $\pm$ 1.17	1.99 $\pm$ 0.27	cm ² /min
Creatinine	1.02 $\pm$ 0.35	2.03 $\pm$ 0.83*	2.26 $\pm$ 0.83**	1.48 $\pm$ 0.64	cm ² /min
Capillary wall transport					
<i>capHC</i> ^a · 10 ⁵	6.7 $\pm$ 1.0	6.5 $\pm$ 1.2	6.9 $\pm$ 1.0	5.3 $\pm$ 0.6***	1/(min·mmHg)
α_{UP}	0.66 $\pm$ 0.10	0.36 $\pm$ 0.14*	0.33 $\pm$ 0.14**	0.44 $\pm$ 0.10***	
<i>capRef</i> for:					
Glucose	0.67 $\pm$ 0.10	0.38 $\pm$ 0.13*	0.35 $\pm$ 0.14**	0.45 $\pm$ 0.10***	
Sodium	0.66 $\pm$ 0.10	0.37 $\pm$ 0.14*	0.34 $\pm$ 0.14**	0.45 $\pm$ 0.10***	
Urea	0.66 $\pm$ 0.10	0.36 $\pm$ 0.14*	0.34 $\pm$ 0.14**	0.44 $\pm$ 0.10***	
Creatinine	0.67 $\pm$ 0.10	0.38 $\pm$ 0.14*	0.34 $\pm$ 0.15**	0.45 $\pm$ 0.10***	
<i>capOsmCond</i> · 10 ⁵	4.6 $\pm$ 1.2	2.5 $\pm$ 1.0*	2.5 $\pm$ 1.2**	2.4 $\pm$ 0.4***	1/(min·mmHg)
<i>capPS</i> ^a for:					
Glucose	0.02 $\pm$ 0.01	0.04 $\pm$ 0.01*	0.05 $\pm$ 0.01**	0.03 $\pm$ 0.01	1/min
Sodium	0.08 $\pm$ 0.03	0.24 $\pm$ 0.12*	0.27 $\pm$ 0.13**	0.15 $\pm$ 0.07	1/min
Urea	0.05 $\pm$ 0.02	0.11 $\pm$ 0.03*	0.12 $\pm$ 0.03**	0.08 $\pm$ 0.02	1/min
Creatinine	0.03 $\pm$ 0.01	0.06 $\pm$ 0.02*	0.06 $\pm$ 0.01**	0.04 $\pm$ 0.01	1/min
Other					
Peritoneal absorption	1.4 $\pm$ 0.5	2.4 $\pm$ 1.4	1.6 $\pm$ 0.7	4.5 $\pm$ 0.1***	mL/min

*P < 0.05 UFF versus NUF group, **P < 0.05 UFF HDR versus NUF group. ***P < 0.05 UFF HAR versus NUF group, in case Mann-Whitney test applied irrespectively to the insufficient size of the sample.

^aValues at the steady state, not inflated by vasodilation, which corresponds to the values at the end of peritoneal dwell.

the tissue and across the capillary wall, were found between patients with NUF and UFF (see Table 2). The estimated values of peritoneal absorption rate for UFF did not differ statistically from those calculated for NUF and remained in agreement with the values calculated based on classical membrane model (K_E). Values >4 mL/min were observed for patients from HAR group, and normal values of around 1.6 mL/min in HDR patients (Table 2).

Interstitial transport

In UFF patients compared with NUF, there was a 56% decrease in *tisHC* and an increase of effective tissue diffusivity for glucose by 34% and creatinine by 99%, while changes for sodium and urea were not significant. The *tisRef* remained statistically unchanged although there was a tendency for decreased values in UFF group versus NUF ($P = 0.07$). The tissue lymphatic absorption rate was increased by 54% in UFF when compared with NUF. Similar changes were found in HDR as in the whole UFF group, whereas in HAR subgroup, the mentioned changes were not observed or less pronounced (Table 2).

Capillary wall transport

Significant alterations of the transport properties across capillary wall were found in UFF patients when compared with NUF. The α_{UP} decreased in UFF patients by 45, 50 and 33% in whole UFF, HDR and HAR group, respectively, compared with NUF (Table 2). This also indicates corresponding increase of the fraction of small pores through which small solutes are

mainly transported. In consequence, a 2-fold increase of solutes permeability across the capillary wall and a decrease by 50% of solutes reflection coefficient of the capillary wall in the whole UFF and HDR groups was observed as compared with NUF. The small number of patients did not allow statistical conclusions on the difference between HAR and NUF group; however, the results suggest that there were significant changes in solutes reflection coefficient but no major changes in permeabilities of the capillary wall. Furthermore, the values of the hydraulic conductance of the capillary wall from UFF group did not differ from the corresponding ones for NUF, whereas for patients from HAR group, decreased values of hydraulic conductance (by 21%) were observed. The above-mentioned changes in the transport properties across capillary wall resulted in decreased values of *capOsmCond* by 46, 46 and 47% for whole UFF, HDR and HAR groups, for glucose respectively, when compared with NUF (Table 2).

Peritoneal transport

In order to present how the local changes of interstitial and capillary wall transport properties translate into the alteration of the global PTS parameters, as typically reported in the studies that apply a membrane approach, the final fluid and solutes penetrations depth as well as the peritoneal transport parameters were calculated and presented in Supplementary data, Table S1. The penetration depths of fluid and solutes in the peritoneal tissue were lower in UFF and HDR groups, but not in HAR when compared with NUF, indicating shallower

impact of the PD exchange on the peritoneal tissue in HDR group than in NUF and HAR groups (Supplementary data, Table S1, Figures S2 and S3). The lower values of *tisHC* in UFF patients resulted in a decrease of *peritHC* (see Table 2 and Supplementary data, Table S1). Moreover, the increase of solutes tissue diffusivity and solutes permeabilities of the capillary wall results in a significant increase of the PTS diffusive coefficients, *KBDs* (PSs), for all solutes, in UFF and HDR groups, but not HAR when compared with NUF patients (Table 2 and Supplementary data, Table S1). The decrease of glucose reflection coefficient and osmotic conductance of the peritoneal membrane was found in UFF and HDR groups versus NUF (Supplementary data, Table S1).

The changes in transport properties of both PTS components were associated with alterations of tissue profiles for NUF, HDR and HAR groups (Supplementary data, Figures S1–S3). The increase of interstitial pressure close to the peritoneal cavity was higher in HAR than in HDR group, and initially the lowest in NUF became the highest after 3 h of peritoneal dwell (Supplementary data, Figures S2 and S3). The initial solutes concentration profiles and penetration depths in the tissue remained similar among all groups (Supplementary data, Figure S1). Later on, lower concentration profiles for glucose, and higher profiles of sodium, urea and creatinine were found in UFF versus NUF group (Supplementary data, Figures S2 and S3). A transient dip in the interstitial sodium concentration profile close to the peritoneal cavity was found during the initial dwell time, mostly marked in NUF (Supplementary data, Figure S1).

DISCUSSION

The present study provides direct functional evidence that alterations of peritoneal transport properties in patients with UFF are due to alterations occurring both within the capillary wall and the tissue barrier. Although different types of alterations may occur simultaneously in the same patient, it is the combined effects of these local changes that lead to the clinically observed alterations of the PTS properties.

Capillary wall transport

The functional decrease of aquaporin fraction (α_{UP}) found in UFF patients remains in agreement with studies showing decreased free water transport and less marked sodium dip in UFF patients [1, 4, 6]. The decrease of α_{UP} and increase of small pore fractions (α_{SP}) indicates increase of small solutes transport relatively to the free water transport. The functional character of the model does not provide information on the possible reasons, which might be related to decreased number of aquaporins or increased number of transport pathways for small solutes (blood capillaries become more leaky). With minor changes in *capHC*, the decrease (by 45%) of α_{UP} leads to decrease by 48% of glucose osmotic conductance through ultra-small pores, doubled glucose osmotic conductance through small pores, and as a consequence, decrease (by 46%) of the overall glucose osmotic conductance of the capillary wall in UFF patients (Table 2).

Interstitial transport

The peritoneal transport of fluid and solutes through the tissue was found to be altered in UFF patients. The *tisHC* in UFF patients was significantly lower, which is difficult to explain. In contrast, the small solute transport was relatively facilitated as suggested by the increase of solutes tissue diffusivity and decrease of solutes reflection coefficient of the tissue. Increased values of tissue lymphatic absorption rate (in 9 out of 11 UFF patients) suggest that the long-term exposure of peritoneal tissue to increased tissue hydration may have promoted this mechanism, preventing local oedema.

The alterations of local peritoneal transport properties influence tissue transport. In UFF patients, the inflow of water into the tissue was more rapid but persisted for shorter time period (Supplementary data, Figures S1–S3). In consequence, although the fluid penetration depths were similar for NUF and UFF groups, higher profiles of interstitial hydrostatic pressure close to the peritoneal cavity during the initial minutes, and slightly lower profiles during further hours of peritoneal dwell, were observed (Supplementary data, Figures S1–S3). The increased solutes tissue diffusivity results in lower glucose concentration and penetration depth in the tissue and faster equilibration of urea and creatinine profiles in patients with UFF (Supplementary data, Figures S2 and S3). Local, transient dilution of the sodium concentration in the tissue (close to the peritoneal cavity), caused by the initial inflow of sodium-free fluid into the tissue through the ultra-small pores, was less pronounced in UFF patients and persisted for a shorter time (Supplementary data, Figures S1–S3).

Peritoneal transport

The values of global, effective parameters for PTS, approximated from local parameters of both transport barriers, remained in agreement with previous studies that applied a membrane approach (Supplementary data, Table S1) [22–26]. We found that HDR patients had decreased fluid solutes penetration depths, decreased peritoneal hydraulic conductance and increased solutes peritoneal membrane diffusive coefficients, whereas in patients from HAR group, these changes were not so much pronounced, Supplementary data, Table S1, as reported by others [2, 27]. In addition, distributed modelling supports current knowledge on UFF by allowing to relate those alterations with the corresponding changes within both barriers. In particular, the lower values of glucose osmotic conductance of the peritoneal membrane ($peritOsmCond = peritHC \cdot peritRef$), found in our study in UFF patients, were related to the lower values of both product components: *peritHC* and glucose diffusive transport parameter of the peritoneal membrane (*peritPS*) (Supplementary data, Table S1). The lower values of the glucose osmotic conductance of the peritoneal membrane suggest lower effectiveness of the osmotic force across peritoneal membrane in UFF versus NUF patients (Supplementary data, Table S1) also reported by others [1, 7, 27, 28]. In addition, the distributed approach suggests that the observed lower *peritHC* in UFF patients was mostly caused by decreased *tisHC* (possibly due to fibrosis), whereas the decrease of glucose reflection coefficient of the

peritoneal membrane (*peritRef*) was mainly related to the lower glucose *capRef* (related to the changes of α_{UP} and α_{SP}) (Table 2, Supplementary data, Table S1) [2, 29–31]. Finally, higher solutes diffusive transport parameters of the peritoneal membrane (*peritPS*) were caused by increased *tisDif* across both barriers (Table 2, Supplementary data, Table S1) [2, 29–31].

Limitations

A small group of patients undergoing CAPD with conventional, glucose-based dialysis fluids. As 4-h PET with 3.86% glucose fluid was not performed, the clinical criteria of UFF used versus ISPD definition of UF <400 mL was not addressed. The relation between interstitial fluid volume and pressure was based on experiments in non-uraemic animals while all other functional formulas were obtained for uraemic PD patients, and transport parameters for capillary wall and tissue, lymphatic absorption, etc. were assessed individually.

In summary, the present study shows that alterations of the individual peritoneal transport properties in patients with UFF are caused by changes occurring both within the capillary wall and the tissue barrier, typically simultaneously, influencing both solute and fluid transport within the tissue. In comparison with patients with NUF, the patients with UFF were found to have: (i) increased solute diffusivity in the two barriers, capillary wall and tissue; (ii) decreased *tisHC*; (iii) increased tissue lymphatic absorption rate (irrespective of direct absorption of peritoneal fluid); and (iv) a functional decrease in the fraction of the ultra-small pores of the capillary wall.

SUPPLEMENTARY DATA

Supplementary data are available at [ndt online](http://ndt-online).

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AUTHORS' CONTRIBUTIONS

J.S-P. and J.W. were responsible for study conception and design. J.S-P., J.P., M.F.F., B.L. and J.W. were responsible for analysis and interpretation of the data. J.S-P. and J.P. were responsible for the preparation of figure and analysis of statistics. J.S-P., J.P., M.F.F., B.L. and J.W. were responsible for drafting the article. J.S-P., J.P., M.F.F., B.L. and J.W. were responsible for revising and approving the article.

CONFLICT OF INTEREST STATEMENT

B.L. is employed by Baxter Healthcare Corporation.

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Intradialytic kinetics of middle molecules during hemodialysis and hemodiafiltration

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ABSTRACT

Background. The kinetics of β_2 -microglobulin during hemodialysis and hemodiafiltration is well described by a two-compartment model where clearance by the dialyzer is from a central compartment volume that approximates plasma volume and a total distribution volume that approximates extracellular fluid volume. The kinetics of middle molecules with molecular weights larger than β_2 -microglobulin have not been extensively studied.

Methods. Intradialytic plasma concentrations and overall dialyzer clearances of β_2 -microglobulin (11.8 kD), myoglobin (16.7 kD) and complement factor D (24.4 kD) were used to estimate three kinetic parameters from a two-compartment model, namely intercompartmental clearance, central compartment volume and total distribution volume, in hemodialysis patients; these data were collected during two clinical trials of medium cut-off dialyzers (with extended middle molecule removal) during hemodialysis and high-flux dialyzers during hemodialysis and hemodiafiltration. In the current exploratory analyses, the kinetic parameters from all dialyzers were combined. Overall dialyzer clearance was evaluated by total mass removed in the dialysate.

Results. In total, 345 sets of kinetic parameters from 35 patients were determined. Intercompartmental clearance and central compartment volume for myoglobin and complement factor D were smaller ($P < 0.001$) than those for β_2 -microglobulin. Independent of middle molecule, intercompartmental clearance and central compartment volume were associated with overall dialyzer clearance ($P < 0.001$), but total distribution volume was not ($P = 0.083$).

Conclusions. A two-compartment kinetic model can only describe intradialytic kinetics of middle molecules with molecular weights larger than β_2 -microglobulin if the central compartment is small and dependent on overall dialyzer clearance.

Keywords: clearance, compartment model, hemodialysis, medium cut-off dialyzers, middle molecules

INTRODUCTION

The clinical trial interventions during the Hemodialysis (HEMO) Study were based on the assumption that patient outcomes depend on the level of uremic toxin removal for both small water-soluble solutes (urea as surrogate) and middle