

# Mathematical Modeling of Different Molecule Removal on On-Line Haemodiafiltration: Influence of Dialysis Duration and Infusion Flow

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## Key Words

Dialysis adequacy · Mathematical modeling · Online haemodiafiltration · Solute removal

## Abstract

**Background:** In a previous study on a nocturnal, every-other-day online haemodiafiltration scheme, different removal patterns were observed for urea, creatinine,  $\beta_2$ -microglobulin, myoglobin and prolactin. The aim of this study was to evaluate the influence of dialysis duration and infusion flow (Qi) on the removal of different molecular weight (MW) solutes, and to quantify the effect of the different treatments on the kinetics of the solutes by using a classical two-compartment model. **Methods:** This prospective, in-center study was carried out in 10 patients on a nocturnal, every-other-day online post-dilution haemodiafiltration program. Each patient received four dialysis sessions with different conditions, two 4-h sessions (with infusion flows of 50 or 100 ml/min) and two 8-h sessions (with infusion flows of 50 or 100 ml/min). To analyze the solute kinetics, blood samples were obtained hourly during the dialysis treatments and in the first 3 h post-dialysis. **Results:** Removal patterns differed in the molecules studied, which were quantified by means of the two-compartment mathematical model. The main re-

sults show the impact of dialysis duration on the removal of low molecular weight molecules (urea and creatinine), while the impact of Qi is clearly shown for high molecular weight molecules (myoglobin and prolactin). For middle molecular weight solutes, such as  $\beta_2$ -microglobulin, both factors (duration and Qi) enhance the removal efficiency of the dialyzer. **Conclusions:** Our study evaluates experimentally and mathematically how treatment time and infusion flow affect the filtration of solutes of different MW during post-dilution haemodiafiltration. The results provided by the present study should help physicians to select and individualise the most appropriate schedules to deliver an optimum diffusive and convective dialysis dose for each patient.

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## Introduction

Mortality in patients undergoing a conventional dialysis regimen has quadrupled in the general population older than 65 years. New therapeutic regimens are therefore required to improve patient survival, such as increasing dialysis time and/or frequency, and developing techniques with a higher depurative capacity [1, 2]. Multiple publications have evaluated the superiority of long-dura-

tion haemodialysis over conventional therapy in blood pressure control, reduction of left ventricular hypertrophy (LVH), and reduced serum phosphate levels [3–5]. Online haemodiafiltration (OL-HDF) offers an optimal form of extracorporeal treatment for dialysis patients. This technique, which combines diffusion with high convection, provides the highest clearances per unit area for small, medium and large molecules. The same dialysis fluid, free of toxins and pyrogens, is used as a substitution solution. This technique is safe and well tolerated and provides good clinical results [6–8].

In a previous study [9], conversion from 4–5 h thrice weekly OL-HDF to 7–8 h every-other-day OL-HDF in a crossover study with the same or higher convective volume showed excellent clinical tolerance and patient acceptance, adequate social and occupational rehabilitation, better dialysis adequacy, remarkable improvement in nutritional status, regression of LVH, good phosphate and hypertension control, and a marked reduction of phosphate binders and antihypertensive medication. Different patterns of solute removal were observed, which were related to dialysis time, convective volume, and/or the infusion flow rate ( $Q_i$ ). Therefore, long-term, nocturnal, in-center, every-other-day OL-HDF with high convective volume could be an effective therapeutic dialysis scheme that could improve clinical and social-occupational rehabilitation.

Two-compartmental models were first introduced in [10] to reproduce the rebound (the abrupt increase of the solute concentration in blood) observed after dialysis, which cannot be replicated by a one-pool model. These models are the systems of minimal size that exhibit both the concentration decay followed by the post-dialysis rebound. Although they are unable to resemble the real physiology of solute interchange inside the body, they have proved very useful in modeling the observable kinetics of the dialyzed molecules.

The purpose of this study was to evaluate the influence of dialysis duration and infusion flow on the removal of different MW solutes, and to verify the usefulness of two-compartment mathematical models in quantifying the changes in removal kinetics when the type of dialysis is changed.

## Patients and Methods

This single-center, prospective study was performed in 10 anuric and stable haemodialysis patients (nine men and one woman), with a mean age of  $50.5 \pm 17$  (in the range 28–78). The patients were receiving nocturnal every-other-day OL-HDF and the mean treatment length was  $40.7 \pm 32$  months. The underlying renal dis-

eases were chronic glomerulonephritis (one patient), diabetic nephropathy (one patient), polycystic kidney disease (two patients), nephroangiosclerosis (three patients), chronic tubulointerstitial nephritis (one patient), and unknown etiology (two patients). All patients signed informed consent forms approved by the Research Committee of the hospital.

The OL-HDF parameters were bicarbonate buffer,  $1.4 \text{ m}^2$  high-flux helixone filter (FX60, Fresenius), blood flow ( $Q_b$ )  $420 \pm 25 \text{ ml/min}$  (in the range 400–450 ml/min), dialysate flow ( $Q_d$ ) 400 ml/min, and a Fresenius 5008 dialysis monitor. Reinfusion was always performed in a postdilutional mode. All patients had native arteriovenous fistulae and 15-gauge needles were used. Each patient received four dialysis sessions, two 4 h sessions (infusion flow 50 or 100 ml/min: 4 h- $Q_i50$  and 4 h- $Q_i100$  sessions) and two 8 h sessions (infusion flow 50 or 100 ml/min: 8 h- $Q_i50$  and 8 h- $Q_i100$  sessions).

To evaluate solute kinetics, blood samples were obtained hourly during the nocturnal treatments and the first 3 post-dialysis hours. Concentrations of urea (60 Da), creatinine (113 Da),  $\beta_2$ -microglobulin (11,800 Da), myoglobin (17,000 Da) and prolactin (23,000 Da) were measured. The reduction ratio percentages (RR) in plasma were calculated by

$$RR = 100 \left[ 1 - \frac{C_f}{C_i} \right], \quad (1)$$

where  $C_i$  and  $C_f$  (mg/ml) are referred to the pre- and end-of-the-dialysis solute concentrations respectively. The equilibrated  $Kt/V$  was calculated for urea as in [11] by means of

$$Kt/V = -\ln \left( \frac{C_{f+1h}}{C_i} - 0.008 t_d \right) + \left( 4 - 3.5 \frac{C_{f+1h}}{C_i} \right) \frac{\Delta W}{DW}, \quad (2)$$

and for the rest of the solutes as

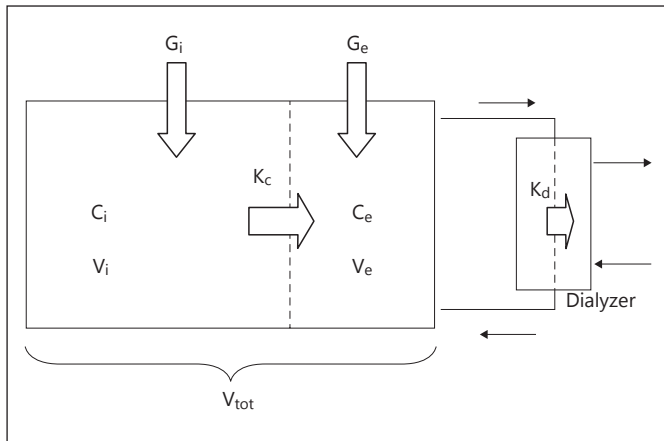
$$Kt/V = -\ln \left( \frac{C_{f+1h}}{C_i} \right), \quad (3)$$

where  $C_{f+1h}$  (mg/ml) is the first of the three post-dialysis concentration measurements used to evaluate the rebound,  $t_d$  (min), refers to the dialysis session duration,  $\Delta W$  (kg), is the interdialytic weight loss and  $DW$  (kg), the post-dialysis body weight. The values  $C_f$  and  $C_{f+1h}$  were corrected for all the solutes except the first two using the method of Bergström and Wehle (B and W) [12]. The corrected data were not used in the mathematical model, since a variation of volume over time was assumed (see next section).

The results are expressed as the arithmetic mean  $\pm$  standard deviation. Each patient served as his or her own control. Student's t-test and the ANOVA test (repetitive data) were used to analyse the differences in quantitative variables. A value of  $p < 0.05$  was considered statistically significant.

### Mathematical Two-Compartment Modeling

A schematic representation of the two-compartment model used in this study is shown in figure 1. The total distribution volume of each solute  $V_{tot}(t_d)$  (ml) was separated in two compartments. What is referred to as external corresponds to the plasma plus part of the rest of the distribution volume, which interchanges any particular solute with the plasma at a high regime, so that the concentration in both subregions can be considered the same. What is referred to as the internal is the rest of the distribution volume, which interchanges the solute with the external compart-



**Fig. 1.** Schematic diagram of the two-pool model.  $V_{tot}$  is the total volume,  $G$  the generation rate,  $C$  the concentration, and  $V_i$ ,  $V_e$  the internal and external compartment volumes. Removal of solutes in the dialyzer is described by a constant rate,  $K_d$ , and  $K_c$  the inter-compartment mass-transfer coefficient.

ment at a lower ratio. As will be seen later, the fraction representing each compartment is found during the fitting, and is allowed to vary with the solute in order to find a better adjusting of the model to the data from the dialysis, including the post-dialysis rebound. We assume that the dialyzer has access to the external compartment, and that the generation of the solutes takes place in both of them. The mass balance equations to solve can be written as

$$\frac{d(V_e C_e)}{dt} = K_c (C_i - C_e) - \delta K_d C_e + G_e, \quad (4)$$

$$\frac{d(V_i C_i)}{dt} = -K_c (C_i - C_e) + G_i, \quad (5)$$

where  $C_i$ ,  $C_e$ ,  $V_i$ ,  $V_e$ ,  $G_i$  and  $G_e$  are the internal and external compartment solute concentrations (mg/ml), volumes (ml) and generation rates (mg/min), respectively. Removal of solutes in the dialyzer is described by a constant rate,  $K_d$  (ml/min) and the inter-compartment mass-transfer coefficient is described by  $K_c$  (ml/min). The factor  $\delta$  allows switching from the dialysis ( $\delta = 1$ ) to the post-dialysis ( $\delta = 0$ ) time intervals. Since the patients were anuric, no renal clearance was assumed. Other two-compartment models can be found, for instance, in references [13–17].

Usually, the total distribution volume  $V_{tot}(t_d)$  is taken as the total body water volume for urea and creatinine [18]. In clinical practice, this volume is commonly obtained from anthropometric data (age, sex, height, dry weight, etc.). In the present study, the Watson formula [19] was used to obtain the total water volumes for each patient and treatment. They were averaged to obtain a mean body water  $V_{tot}(t_d)$ , which represented 0.538 times the averaged  $DW$ . These assumptions lead to a urea distribution volume of  $41.64 \pm 0.07$  l, which was also taken for creatinine. For  $\beta_2$ -microglobulin, myoglobin and prolactin,  $V_{tot}(t_d)$  was assumed as 1/3 of the total body water volume ( $\sim 18\%$   $DW$ ), closely related to that reported in [20].

The variation of  $V_{tot}$  over time was considered piecewise linear, namely,

$$V_{tot}(t) = V_{tot}(t_d) (1 - \beta_d(t - t_d)), \quad (6)$$

$$V_{tot}(t) = V_{tot}(t_d) (1 + \beta_p(t - t_d)), \quad (7)$$

(6) and (7) representing the volumes during the dialysis session and the interdialysis time intervals respectively. The slopes  $\beta_d$  and  $\beta_p$  (1/min) are the constant ratios at which  $V_{tot}$  is reduced during the dialysis session and is recovered interdialysis. They are calculated as

$$\beta_d = \frac{[(V_{tot}(0)/V_{tot}(t_d)) - 1]}{t_d}, \quad (8)$$

$$\beta_p = \frac{[(V_{tot}(0)/V_{tot}(t_d)) - 1]}{t_f - t_d}, \quad (9)$$

where  $t_f$  (min) is the total time between consecutive sessions and,  $V_{tot}(0)$ , is the volume at the start of the treatment.

The volume fractions occupied by each compartment were characterised by the dimensionless parameter  $\alpha$ ,  $\alpha = V_e / V_{tot}(t_d)$  and  $1 - \alpha = V_i / V_{tot}(t_d)$  being thus  $V_{tot} = V_e + V_i$ . In this way the size of both compartments depends on the solute.

Constant generation rates were considered to take place in both pools, proportional to the compartment volumes, that is,  $G_e = \alpha G$  and  $G_i = (1 - \alpha)G$  with  $G$  the total generation in the distribution volume. It was assumed that the 4 h-Qi50 OL-HDF sessions had reached a stationary regimen. Therefore,  $G$  was taken to be such that the value of  $C_e$  at  $t_f$  coincided with that at the beginning of the current OL-HDF session. Since the generation does not depend on the treatment type, the value of  $G$  was taken to be the same for the four treatments and equal to that found for the 4 h-Qi50 session. This means that

$$G = f_G \frac{C_e(0)V_{tot}(0) - C_e(t_r)V_{tot}(t_r)}{t_f - t_r}, \quad (10)$$

where  $t_r$  (min) is  $t_d$  plus the time after the treatment for which concentration data was sampled to evaluate the rebound. The prefactor  $f_G \approx 1$  was used to fine-tune  $G$ . If  $f_G = 1$ , the concentration at  $t_f$ , computed after fitting  $K_d$ ,  $K_c$  and  $\alpha$ , can differ slightly from that at the initial time. Therefore,  $G$  must be modified by a small amount, which is adjusted iteratively. Other ways to compute the generation rate  $G$  based on  $Kt/V$  and protein catabolic rate (PCR) can be found in [21, 22]. However, we have checked that slight changes in the generation produce small variations in the fitted parameters  $K_d$ ,  $K_c$  and  $\alpha$ .

To enable comparison among different treatments and solutes, the concentrations were normalised to the initial OL-HDF session value. Since the two compartments were assumed to be in equilibrium at the initial time,  $C_e(0) = C_i(0)$ . The relative concentrations are  $\bar{C}_e = C_e(t) / C_e(0)$  and  $\bar{C}_i = C_i(t) / C_e(0)$ , and the equations for their evolution are

$$\alpha \bar{V}_{tot} \frac{d\bar{C}_e}{dt} = \bar{K}_c (\bar{C}_i - \bar{C}_e) - \delta \bar{K}_d \bar{C}_e - \alpha \frac{d\bar{V}_{tot}}{dt} \bar{C}_e + \alpha \bar{G}, \quad (11)$$

$$(1 - \alpha) \bar{V}_{tot} \frac{d\bar{C}_i}{dt} = -\bar{K}_c (\bar{C}_i - \bar{C}_e) - (1 - \alpha) \frac{d\bar{V}_{tot}}{dt} \bar{C}_i + (1 - \alpha) \bar{G}, \quad (12)$$

where  $\bar{K}_c = K_c / V_{tot}(t_d)$ ,  $\bar{K}_d = K_d / V_{tot}(t_d)$ ,  $\bar{G} = G / C_e(0) V_{tot}(t_d)$  and  $\bar{V}_{tot}(t) = V_{tot}(t) / V_{tot}(t_d)$ , are the normalized mass-transfer coefficient, dialyzer clearance, generation and volume, respectively. In addition  $d\bar{V}_{tot} / dt = -\beta_d$  and  $d\bar{V}_{tot} / dt = \beta_p$ , as stated in (6) and (7).

**Table 1.** Pre- and post-dialysis body weight, hematocrit, interdialytic weight gain, replacement volume, and monitor-provided Kt obtained by ionic dialysance for each treatment

	4 h-Qi50	4 h-Qi100	8 h-Qi50	8 h-Qi100
Body weight, kg				
Pre-dialysis	80.45±12	81.00±12	80.56±12	80.34±12
Post-dialysis	77.48±11	77.49±11	77.23±11	77.36±11
Hematocrit, %				
Pre-dialysis	33.9±5.5	31.5±3.6	33.9±4.9	33.4±4.3
Post-dialysis	40.2±8.1	39.6±7.5	39.4±4.6	38.7±4.7
Interdialytic weight gain, kg	2.97±1.0	3.51±1.0	3.33±1.0	2.98±0.9 <sup>d</sup>
Replacement volume, l	11.7±0.7	21.1±1.7 <sup>a</sup>	22.7±1.0 <sup>a, c</sup>	43.1±3.4 <sup>a, c, e</sup>
Kt <sub>urea</sub> , l	56.7±2.7	57.8±3.9	104.3±15.1 <sup>a, c</sup>	111.2±7.3 <sup>a, c, f</sup>

<sup>a</sup>  $p < 0.01$ ; <sup>b</sup>  $p < 0.05$  with respect to 4 h-Qi50 (ANOVA repeated measures). <sup>c</sup>  $p < 0.01$ ; <sup>d</sup>  $p < 0.05$  with respect to 4 h-Qi100 (ANOVA repeated measures). <sup>e</sup>  $p < 0.01$ ; <sup>f</sup>  $p < 0.05$  with respect to 8 h-Qi50 (ANOVA repeated measures).

The fraction of the external to the total volume is included as a free parameter to be determined because the post-dialysis rebound time of the molecules is related to  $\alpha$  (in addition to  $\bar{K}_c$ ). By taking  $\delta = 0$  in Eq. (11), neglecting  $\bar{G}$  in Eqs. (11–12) and assuming  $\beta_p \approx 0$ , because the rebound time is a small fraction of the total interdialysis interval, it is straightforward to obtain

$$\bar{C}_i(t - t_d) - \bar{C}_e(t - t_d) = (\bar{C}_i(t_d) - \bar{C}_e(t_d)) \exp(-\bar{K}_c(t - t_d)/\alpha(1 - \alpha)), \quad (13)$$

for  $t > t_d$ . Then, the rebound time,  $\Delta t_{reb}$  (min), defined as the time required to reduce  $\Delta \bar{C}(t_d) = \bar{C}_i(t_d) - \bar{C}_e(t_d)$  to, for instance, one tenth is:

$$\Delta t_{reb} = \ln(10) \frac{\alpha(1 - \alpha)}{\bar{K}_c} = \ln(10) \frac{\alpha(1 - \alpha)}{K_c} V_{tot}(t_d), \quad (14)$$

therefore, solutes for which  $\alpha$  is small or large (close to 0 or 1), or  $\bar{K}_c$  is large will have a short rebound time. Hence, it can easily be seen that the height of the rebound, that is, the variation of  $\bar{C}_e$  during the rebound time, is

$$h_{reb} = 0.9(1 - \alpha)\Delta \bar{C}(t_d), \quad (15)$$

which in turn is a decreasing function of  $\bar{K}_c$  (see equation (13)). Therefore, the lower the value of  $\alpha$  and  $\bar{K}_c$  the higher the rebound. From our results it seems that three hourly post-dialysis samples are enough to estimate the parameters of the rebound.

To check the model, the amount of mass extracted,  $M_e$  (mg), can be calculated from the time evolution of the external concentration by means of

$$M_e = K_d \int_0^{t_d} C_e(t) dt, \quad (16)$$

and can be obtained by adding the equation

$$\frac{dM}{dt} = K_d C_e(t)$$

with initial condition  $M(0) = 0$  to the system (11–12). Then  $M_e = M(t_d)$ .

The three parameters,  $\bar{K}_d$ ,  $\bar{K}_c$ , and  $\alpha$ , were computed by fitting the model to the concentration data, averaged among the patients,

to obtain the kinetic profile of each solute and treatment, and to study the improvement of the dialyzer clearance of the solutes with the increase in treatment time and infusion flow. The parameters were obtained by minimizing the error function

$$\varepsilon(\bar{K}_d, \bar{K}_c, \alpha) = \sum_{j=1}^m (\bar{C}_j - C_j^e)^2, \quad (17)$$

where  $m$  is the total number of measures available at times  $t_j$ ,  $j = 1, \dots, m$  ( $m = 8$  for 4 h and  $m = 12$  for 8 h treatments, including the initial and rebound data),  $\bar{C}_j$  is the value of the computed normalized solute concentration in the external compartment at time  $t_j$  for the given  $\bar{K}_d$ ,  $\bar{K}_c$ , and  $\alpha$ , and  $C_j^e$  is the normalized solute concentration in the patient's blood at the same times. To solve the least squares problem and to obtain the final error function value,  $\varepsilon$ , which is an indicator of the accuracy of the model, the subroutine LMDIF of the MINPACK [23] package implementing the Levenberg-Marquardt algorithm was used. For the time integration, the embedded Runge-Kutta formulas of Dormand and Prince, implemented in the subroutine DOPRI5 [24] were used.

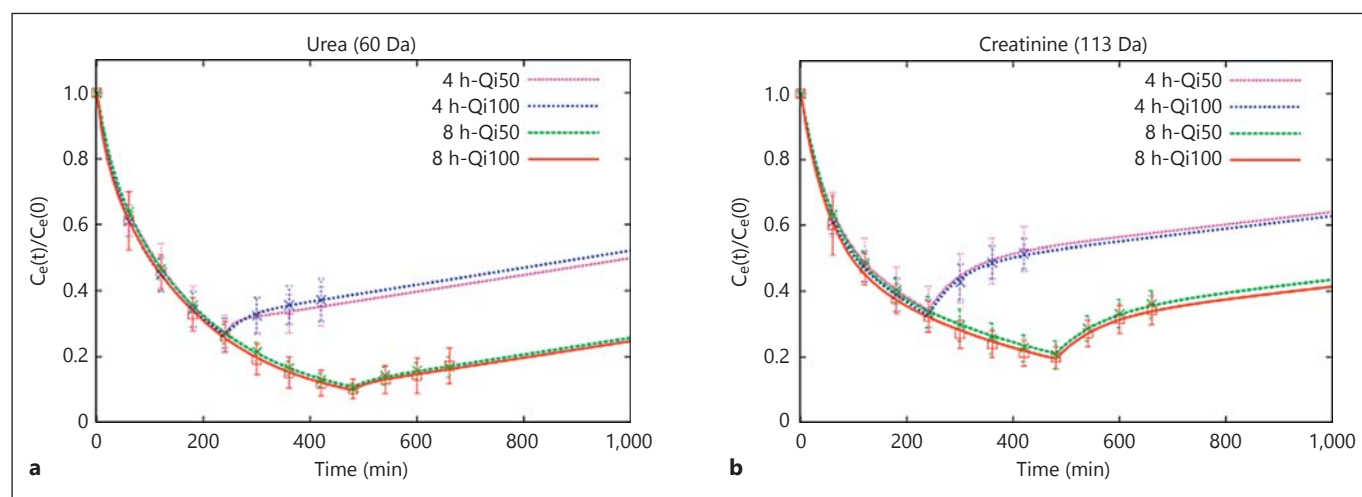
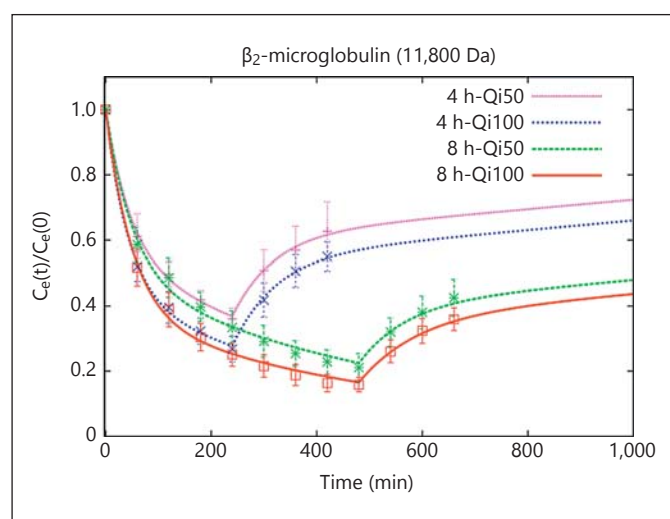
## Results

The patients were randomized to receive different convective volumes and/or dialysis session durations. The convective volume was  $11.7 \pm 0.7$  l in 4 h-Qi50 sessions, which was increased to  $21.1 \pm 1.7$  l,  $22.7 \pm 1.0$  l and  $43.1 \pm 3.4$  l in 4 h-Qi100, 8 h-Qi50 and 8 h-Qi100 sessions, respectively. There were no significant differences in the values of the pre- and post-dialysis body weight and hematocrit. However, there were significant differences in the interdialysis weight gain among 4 h-Qi100 and 8 h-Qi100 treatments (see table 1), and in the marker of the dialysis dose, Kt obtained from ionic dialysance (see also table 1) since the treatment durations were different.

**Table 2.** Reduction ratio and equilibrated  $Kt/V$  for each treatment type and solute

Solute	Reduction ratio (%) / equilibrated $Kt/V$			
	4 h-Qi50	4 h-Qi100	8 h-Qi50	8 h-Qi100
Urea	72.2±5.7/1.33±0.20	72.8±4.3/1.36±0.21	88.8±3.0 <sup>a, c</sup> /2.79±0.43 <sup>a, c</sup>	89.7±2.9 <sup>a, c</sup> /3.02±0.77 <sup>a, c</sup>
Creatinine	65.7±6.6/0.84±0.20	67.1±4.1/0.85±0.13	79.4±4.0 <sup>a, c</sup> /1.26±0.13 <sup>a, c</sup>	80.4±3.1 <sup>a, c</sup> /1.31±0.16 <sup>a, c</sup>
$\beta_2$ -microglobulin	69.9±2.8/0.84±0.12	77.9±3.6 <sup>a</sup> /1.09±0.13 <sup>a</sup>	82.6±3.4 <sup>a, c</sup> /1.34±1.14 <sup>a, c</sup>	86.7±1.9 <sup>a, c, e</sup> /1.52±0.13 <sup>a, c, f</sup>
Myoglobin	34.7±8.2/0.32±0.10	55.5±9.8 <sup>a</sup> /0.63±0.13 <sup>a</sup>	46.0±7.7 <sup>a, c</sup> /0.46±0.15	64.6±5.2 <sup>a, c, e</sup> /0.79±0.13 <sup>a, e</sup>
Prolactin	28.9±6.8/0.28±0.11	45.5±14 <sup>a</sup> /0.44±0.17	32.8±6.7 <sup>c</sup> /0.34±0.11	50.0±4.5 <sup>a, e</sup> /0.52±0.17 <sup>a</sup>

<sup>a</sup>  $p < 0.01$ ; <sup>b</sup>  $p < 0.05$  with respect to 4 h-Qi50 (ANOVA repeated measures). <sup>c</sup>  $p < 0.01$ ; <sup>d</sup>  $p < 0.05$  with respect to 4 h-Qi100 (ANOVA repeated measures). <sup>e</sup>  $p < 0.01$ ; <sup>f</sup>  $p < 0.05$  with respect to 8 h-Qi50 (ANOVA repeated measures).

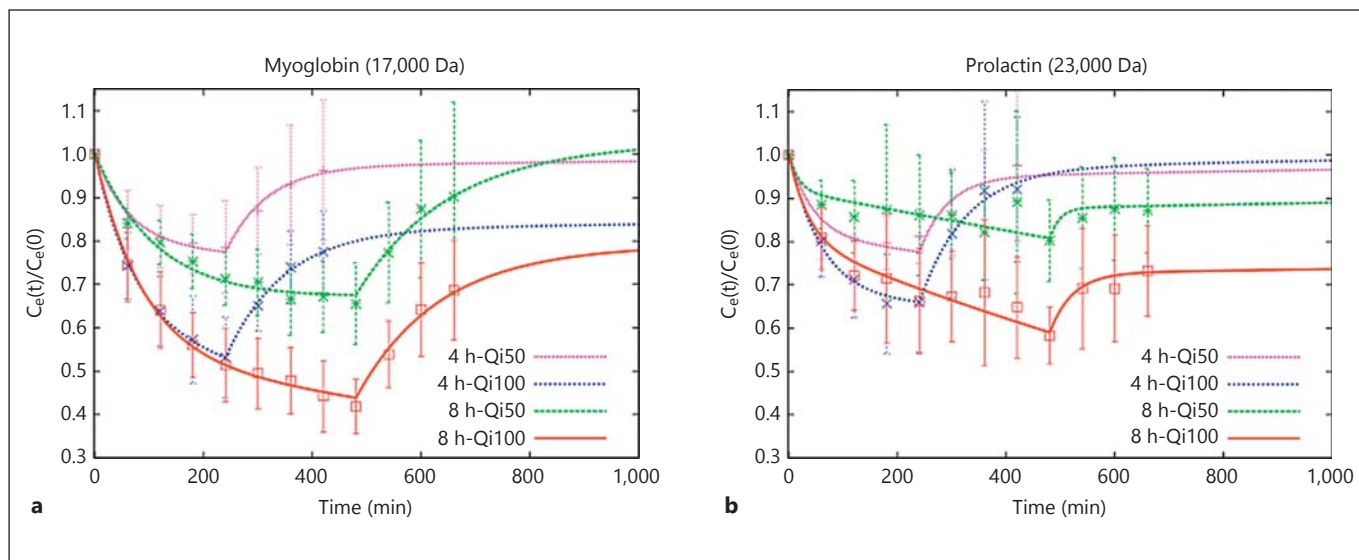
**Fig. 2.** Evolution of the normalized concentrations versus time for (a) urea and (b) creatinine. The symbols correspond to the sampled data, and the lines to the computed profiles. The treatment type is indicated by the labels.**Fig. 3.** Same as figure 2 for  $\beta_2$ -microglobulin.

### Solute Removal

The influence of treatment time and infusion flow on the RR and the equilibrated  $Kt/V$  of the different MW solutes studied is summarized in table 2. Only the initial and post-dialysis concentrations measured were used to compute the RR presented. The results obtained from the numerical model, using the time evolution of the data, are presented in the next section.

The mean values for urea and creatinine were significantly increased when the treatment duration was changed. By increasing the treatment time from 4 h to 8 h, the RR for urea increased by around 17% and for creatinine by 14%. The change in the infusion flow improved the RR for both solutes by only 1%, which was below the error of the mean value of the RR.

A different pattern was observed in the  $\beta_2$ -microglobulin RR, which significantly increased after changes in



**Fig. 4.** Same as figure 2 for (a) myoglobin and (b) prolactin.

both Qi and treatment duration. A time variation from 4 h-Qi50 to 8 h-Qi50 increased the convective volume from 11.7 l to 22.7 l, which increased the RR by 13%, whereas changing the convection from 4 h-Qi50 to 4 h-Qi100 enhanced the RR by around 8%.

Another pattern was observed in myoglobin and prolactin RR, which significantly increased when Qi100 was used. By doubling the treatment time and maintaining the same infusion flow, the RR increased by approximately 10% for myoglobin and by 4% for prolactin. The influence of the infusion flow was clearly marked, improving the RR for myoglobin by 20% and that for prolactin by 17%.

#### Mathematical Two-Compartmental Modeling

The evolution of the fitted external volume concentration of each solute between the beginning of the OL-HDF session and a large enough post-dialysis time to show the rebound (lines), together with the measured data (symbols) are shown in figures 2–4.

The computed  $K_d$ ,  $K_c$ ,  $\alpha$ , the parameters of the rebound  $\Delta t_{reb}$  and  $h_{reb}$ , and the calculated  $M_e$  are shown in table 3. The agreement of the computed results with the sampled data is clearly seen from the plots and the values of the error function given in table 4.

Urea and creatinine kinetics were found to be almost independent of the infusion flow. The concentration decay of the four curves overlapped during the first 4 h of treatment for both solutes (see fig. 2). As is well known, the main difference between these two mole-

cules is that urea hardly shows a rebound. Since the value of  $K_c$  is very high (see table 3), the two compartments are always near equilibrium. Consequently, the four values of  $K_d$  for urea are very similar (see the first row of the table). The results for creatinine were similar, but, in contrast, it already displayed a significant rebound height due to the substantial decrease of  $K_c$ . The variations of  $K_d$  for both solutes were below the error in their determination. Therefore, an improvement of the RR can be obtained only by increasing the dialysis time, assuming the same dialyzer and blood/dialyzate flow conditions.

For  $\beta_2$ -microglobulin, the value of the infusion flow separates the kinetic behavior (fig. 3). This was the first of the studied solutes to show this result, as a consequence of the much larger MW. The modeled concentration decay was more abrupt, and the external concentration was always lower for Qi = 100 ml/min than for Qi = 50 ml/min. When the infusion flow was increased, the computed  $K_d$  was 40% higher for the 4 h treatment and 27% for that of 8 h. In contrast, the increase in dialysis time produced small variations of  $K_d$ . The improvement in RR obtained by increasing the dialysis time was still higher than that produced by augmenting Qi (see fig. 3). Since  $K_c$  and  $\alpha$  were smaller than for creatinine, the height of the rebound was more pronounced.

For myoglobin and prolactin, the value of the infusion flow clearly separated the kinetic behavior, improving RR (fig. 4). For myoglobin, treatments with Qi = 100 ml/min showed stronger decay, reflected in the strong variation

**Table 3.** Fitted values of dialyzer clearance,  $K_d$ , inter-compartment mass transfer,  $K_c$ , external volume ratio,  $\alpha$ , the calculated post-dialysis rebound time,  $\Delta t_{reb}$ , height percentage,  $h_{reb}$ , and extracted mass,  $M_e$ , for each treatment type and solute

	4 h-Qi50	4 h-Qi100	8 h-Qi50	8 h-Qi100
$K_d$ , ml/min				
BUN	271	272	262	277
Creat.	188	201	171	183
$\beta_2$ -m	48	67	51	65
Myogl.	4	18	1	13
Prolac.	6	6	6	13
$K_c$ , ml/min				
BUN	834	321	341	599
Creat.	162	175	116	126
$\beta_2$ -m	39	37	34	29
Myogl.	14	21	2	12
Prolac.	22	11	54	41
$\alpha$				
BUN	0.33	0.51	0.56	0.38
Creat.	0.43	0.41	0.41	0.39
$\beta_2$ -m	0.32	0.33	0.32	0.35
Myogl.	0.09	0.21	0.02	0.16
Prolac.	0.09	0.07	0.08	0.15
Rebound $\Delta t_{reb}$ , min/ $h_{reb}$ , %				
BUN	25/4	74/6	69/2	37/2
Creat.	145/15	132/16	199/13	180/12
$\beta_2$ -m	176/25	188/27	204/18	250/20
Myogl.	176/20	246/30	384/34	346/35
Prolac.	120/17	198/31	42/7	96/14
$M_e$ , g				
BUN	13.53	13.66	18.30	16.61
Creat.	1.65	1.80	2.34	2.30
$\beta_2$ -m	0.14	0.18	0.23	0.24
Myogl.	0.30	1.15	0.15	1.50
Prolac.	0.02	0.02	0.04	0.06

BUN = Blood urea nitrogen; Creat. = creatinine;  $\beta_2$ -m =  $\beta_2$ -microglobulin; Myogl. = myoglobin; Prolac. = prolactin.

**Table 4.** Error function values,  $\varepsilon$  ( $\times 10^{-3}$ ), for each treatment type and solute

	4 h-Qi50	4 h-Qi100	8 h-Qi50	8 h-Qi100
$\varepsilon$ ( $\times 10^{-3}$ )				
BUN	0.07	0.14	0.10	0.31
Creat.	0.22	0.26	0.34	0.57
$\beta_2$ -m	0.60	0.49	2.90	1.76
Myogl.	0.63	0.24	2.51	1.40
Prolac.	5.15	1.21	7.58	5.93

BUN = Blood urea nitrogen; Creat. = creatinine;  $\beta_2$ -m =  $\beta_2$ -microglobulin; Myogl. = myoglobin; Prolac. = prolactin.

of  $K_d$ , which is more than 4 times that obtained for Qi = 50 ml/min as can be seen in table 3. For prolactin, the error function value increased a lot, and therefore, the fit was not as good as before, due to a larger dispersion of the samples. These were the first two solutes for which 4 h treatments were more efficient than those of 8 h, due to the enlarged infusion flow (see fig. 4 and table 2). Moreover, without convection, standard treatments would not be able to reach significant RR.

## Discussion

Solute and fluid removal are the major goals of dialysis. Reduction of elevated pre-dialysis uremic toxin levels may prevent or postpone the onset of dialysis-related complications. Resistance to diffusion within tissues and organs creates solute disequilibrium gradients. The global resistance to diffusion can be quantified as the inter-compartment mass-transfer coefficient,  $K_c$ , which is molecular size-sensitive. However, as a parameter obtained from a simple two-pool model, it is impossible to assess its direct relationship with a particular mass-transfer coefficient through the body tissues. Nevertheless, our study allowed us to confirm distinct patterns of solute removal, to estimate  $K_d$ ,  $K_c$ , the internal and external volume fractions given by the fitted parameter  $\alpha$ , the post-dialysis rebound time duration  $\Delta t_{reb}$ , and height percentage  $h_{reb}$ , and calculate the solute extracted mass  $M_e$  to check the matching of the calculations and the experimental data.

OL-HDF is a removal technique that is mainly governed by its duration, and blood, dialysate, ultrafiltration and infusion flows. Furthermore, the convective volume (CV) is used as a marker of convective efficiency. Canaud and Bowry [25] reported that a threshold of CV of 19–22 l/session provides significant beneficial effects to patients. This parameter, however, as a combination of time and convection, may hinder how these treatment conditions separately affect the clearance of some uremic substances. Tattersall and Ward [26] link the convective efficiency as a relation between the total processed blood (blood flow times time) and CV. In this case, convective transport is achieved when CV is at least 20% of the blood processed. In our case, treatments with Qi = 50 ml/min resulted in a poor CV of approximately 12% of the processed blood, while treatments with Qi = 100 ml/min represented an optimal value of around 21%.

Urea and creatinine clearance, as a marker of small molecules, largely depends on diffusion (time) processes

[27]. In our study, the strong dependence of the removal of these low MW solutes on the treatment time is demonstrated by the minimal improvement due to infusion flow changes. Furthermore, Ficheux et al. [28] studied the influence of convection on small molecule kinetics by adjusting the clearance as a function of the ultrafiltration rate. The study results revealed that convection enhances urea clearance by around 5%, when the ultrafiltration rate was increased from 50 to 100 ml/min in an HF80 dialyzer. Similar enhancements were found for the FX60 filter used in our study (see [29]). A similar behaviour has been obtained for our  $K_d$ , computed from the kinetics, for creatinine, and urea for the 8 h-Qi100 treatment.

The result of  $\beta_2$ -microglobulin removal, as a marker of middle molecule solutes, largely depends on convection processes and the total amount of convective volume [30].  $\beta_2$ -microglobulin clearance was found to be time-dependent in [27], and infusion flow-dependent in [31]. Our study demonstrates the importance of each factor in  $\beta_2$ -microglobulin removal, resulting in an averaged 11% higher RR by doubling the treatment time, and a 6% improved RR by doubling convection. As time and convection have to be considered, the CV value could be a good marker of removal efficiency for this solute. Furthermore, the effect of the infusion flow is clearly apparent in our fitted  $K_d$  values. Kanamori and Sakai [32] estimated a pure diffusive clearance of 30 ml/min for high-performance dialyzers. The convective effect in our study may increase these values in around 30 ml/min. Moreover, our fitted  $\alpha$  value corresponds nearly to the same 1/3 assumed in their study, confirming the importance of leaving it as a free parameter. Furthermore, our computed extracted mass values are similar with the ones presented by Maheshwari et al. [33], demonstrating the validity of the results.

A different pattern was observed for molecules larger than  $\beta_2$ -microglobulin, for which the RRs depend only on the infusion flow and not on the total convection volume. In the case of myoglobin, few previous studies [34, 35] have confirmed the necessity of using the convective dose of OL-HDF or super-high flux membranes [36, 37] to efficiently remove these molecules, whereas both low- and high-flux hemodialysis (LF-HD and HF-HD) resulted in poor or nil removal. We found that 4 h-Qi100 treatments are more efficient in terms of removal (56% RR,  $K_d = 18$  ml/min) than 8 h-Qi50 treatments (46% RR,  $K_d = 1$  ml/min), both with nearly the same convective volume. Furthermore, our fitted clearance values are higher than the conventional ones for high-flux dialyzers ( $K_d = 2.2$  ml/min) reported by Keir et al. [38] for rhabdomyolysis pa-

tients, indicating thus, the necessity of enlarged infusion flows to enhance myoglobin removal. For prolactin, a similar kinetic behavior was found. Despite the poor smoothness of the data, we can conclude from our results, that high infusion flows are needed to efficiently remove this solute, confirming that infusion flow is a better marker of removal than total CV for high MW solutes.

As mentioned in the methods section, the fraction of the external to the total volume,  $\alpha$ , was not fixed *a priori*, as in most kinetics studies, to 1/3 (see [39, 40]). This fraction was obtained from the fitting. We have checked that this strategy strongly improves the adjustment. Moreover,  $\alpha$  characterizes the molecules since, taking into account the error in the samples and, as can be seen in table 3, it is fairly independent of the treatment (except for myoglobin for which the concentration data have a large dispersion among patients). It also determines the shape of the rebound of the external concentration, as shown in equations (14) and (15). The value  $\alpha = 1/3$  is lower than that found in our study for all solutes, except for those with very large MW. Table 3 shows that the higher the MW of the solutes, the lower the value of  $\alpha$ .

The mass of each solute extracted during the different treatments is also included in table 3. In a steady state and having equally spaced dialyses,  $M_e$  would be independent of the intensity or duration of the treatment, but the figures shown in the table indicate that the average blood concentrations would be lower in the case of high molecular-weight solutes and high infusion flow.

In summary, our study evaluated experimentally and mathematically how treatment time and infusion flow affect different MW solutes. The results obtained confirm the impact of dialysis duration on the removal of molecules of low molecular weight (urea and creatinine), while the impact on Qi was clearly shown for the molecules of high molecular weight (myoglobin and prolactin). For middle molecular weight solutes, such as  $\beta_2$ -microglobulin, both factors enhance the removal efficiency of the dialyzer. In-depth analysis of which infusion flow clearly separates the kinetic behavior of each molecule could lead to new treatment strategies, resulting in better and more adequate dialysis. The influence of these parameters on removal efficiency, and understanding of the kinetic behavior of each solute, should help physicians to select the most appropriate schedules to deliver an optimum diffusive and convective dialysis dose. In addition, knowledge of the role of these parameters should help to improve dialyzer technology, reaching higher convective flows and better removal of solutes beyond  $\beta_2$ -microglobulin.



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