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# Analysis of the Dialysis Dose in Different Clinical Situations: A Simulation-Based Approach

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Additional information is available at the end of the chapter

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## 1. Introduction

End Stage Renal Disease (ESRD) is an important public health concern around the globe. It is associated with high morbidity and mortality being Hemodialysis (HD) the main applied therapy. [1]

A recent study (HEMO study) could not show any decrease in the morbidity and/or mortality associated with increases in the dose -expressed as equilibrated Kt/V (eqKt/V)- and/or the flow (comparing high versus low flux, where high flux is defined as a Kt/V of Beta 2 microglobulin (B2M)  $\geq 20$  ml/min) when utilizing the three-times-a-week (3-times/wk HD) schedule therapy. [2]

This led to development of several HD schedules proposals based on the variation of the session time duration (TD) as well as on its weekly frequency (Fr). However, more frequent HD schedules require new indexes to measure the delivered dose. In this context, the Equivalent Renal Clearance (EKR) [Casino y López] [3] and Standard Kt/V (stdKt/V) [Gotch] [4] indexes have been proposed to quantify the dialysis dose for different HD frequency schedules.

The EKR concept equalizes the time-averaged concentration (TAC) of Urea (U) for different therapies which is then normalized by U distribution Volume. Gotch has proposed that the weekly dialysis dose (WDD) is better expressed as standardized kt-V (stdKt/V) when dialysis is more frequent than 3-times/wk. Standard Kt/V combines treatment dose and frequency allowing comparison of intermittent (HD, High flux HD, Hemofiltration,

etc) and continuous (Continuous Ambulatory Peritoneal Dialysis) therapies; the formula is expressed as U generation rate (G) rate divided by the average peak concentration. [4]

$EqKt/V$  is the true dialysis dose per session occurring when U rebound (R), which is related to compartments and flow disequilibrium produced during HD treatment, is completed 30-60 minutes after the end of the HD session.

The determination of  $eqKt/V$  requires the measurement or the “prediction” of the true  $Eq U$  because the value of  $sp$  (single pool) $Kt/V$  - a dimensionless ratio which includes Clearance of dialyzer (K), duration of treatment (TD) and volume of total water of the patient (V) - is greater than the  $Kt/V$  achieved in the patient which is calculated using the immediate postHD blood U concentration.

In the last decade, several formulas were developed to predict  $eq Kt/V$  trying to avoid the extraction of an additional blood sample. The Daugirdas and Schneditz “rate formula” is the most popular and validated equation and it is based in the prediction of  $eqKt/V$  as a linear function of  $spKt/V$  and the rate of dialysis (K/V). [5]

An alternative and robust formula, based in the double pool analysis by Smye, [6] is the equation of Tattersall where he described a soluble time constant: the patient equilibration time ( $t_p$ ). [7]

The majority of these formulas of prediction have been validated in the 3-times/wk HD schedules.

New formulas to predict  $eq Kt/V$  have been recently published. Examples include the  $eqKt/V$  formula based on observations of the HEMO [8] study and two others developed by Leypoldt (based on blood sample analysis during hemofiltration and short and daily HD) [9].

The high accuracy of the extracellular U concentration evolution during and after (UR) an HD session by double pool U kinetic model has been verified in several studies. [10]

Access and cardio-pulmonary recirculation can both influence the UR, but the effect occurs in the first minutes after the end of HD and is considered to be mild. [10]

Several factors other than clearance of U might play a role in morbidity and mortality of hemodialyzed patients.

One of them, recently revised, is the role of the “denominator” to normalize the Kt. The results derived from the HEMO study showed that  $Kt/V$  failed to explain the paradoxical outcomes related to size (underweight versus obese patients) and gender. This factor was considered in the Frequent Hemodialysis Network (FHN) study which is currently underway. The investigators included the body surface area (BSA) as a potential tool for a better normalization of Kt and to allow more appropriate comparison among different HD populations. [11]

Since 1980 the idea of emulating reality in a computer environment by simulation rapidly spread among biomedical researchers, being accepted as one of the most powerful

tools both for understanding phenomenological aspects of a chosen physics or physiological complex and for predicting functional or operative conditions of technological systems. The main concept of this approach relies in numerically solving a mathematical model that governs a chosen physical system, whose the analytical solution is not known or potentially dangerous to reach for a specific application. In spite of many efforts spent in the past for formulating accurate and robust algorithms for solving mathematical models, the effectiveness of that approach heavily dependent on computational resources. This led to only recent widespread use of simulation strategy both scientific and medical problems [12].

A variable volume double-compartment (VVDC) kinetic model can reflect the behavior of different molecules and can be used as a mirror to analyze the profile in vivo by taking blood samples during the HD procedure. [13]

In this scenario, the computational simulation including all the variables which affect the dialysis procedure can be a safe and useful tool to mimic many treatment schemes to help improve our knowledge of the dialysis therapy. [14]

The aim of this study is to utilize a variable volume double-compartment (VVDC) kinetic model to simulate:

1. Several clinical situations that allow comparison between the true  $eqKt/V$  and all the developed predictors, including the effect of increasing the TD and Fr.
2. Changes in  $Kt/V$ , EKR and  $stdKt/V$  related to changes in TD and Fr.
3. Comparison between using V with BSA to normalize K.

## 2. Materials and methods

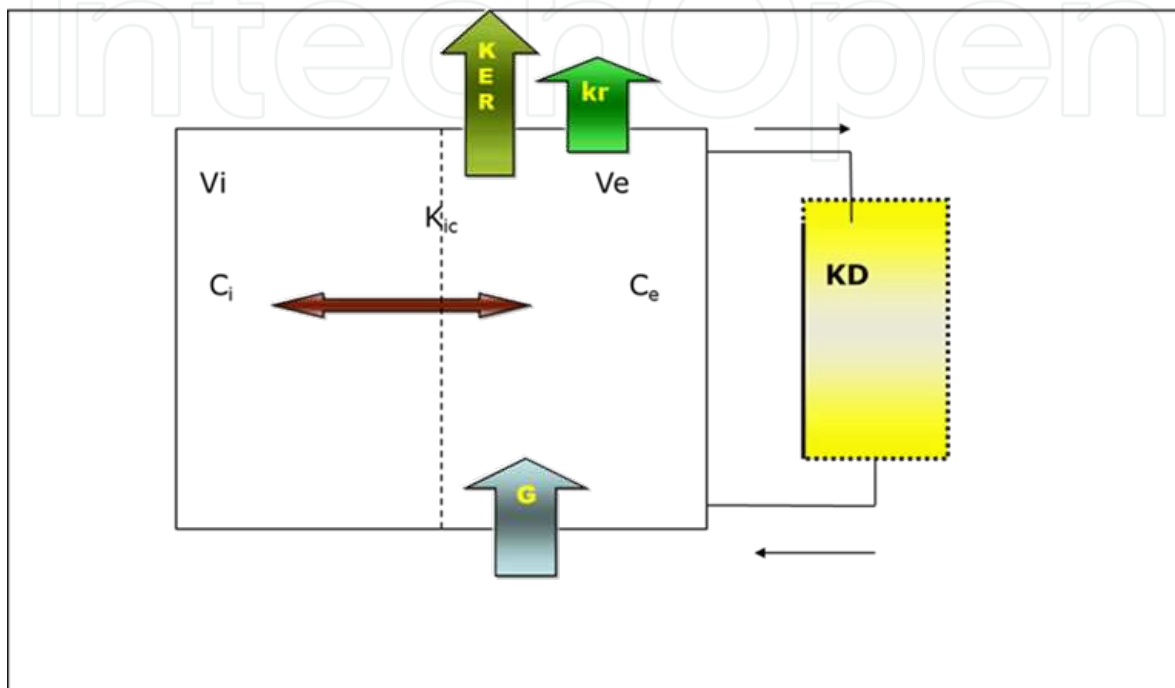
### 2.1. Simulation and analysis

A variable volume double-compartment (VVDC) kinetic model has been implemented based on the existing models of the U concentration behaviour. The model is described in Figure 1 and the equations are as follows:

$$\frac{d(V_e C_e)}{dt}(t) = G - K_c(C_e(t) - C_i(t)) - C_e(t)(K_e(t) + K_r + K_d) \quad (1)$$

$$\frac{d(V_i C_i)}{dt}(t) = K_c(C_e(t) - C_i(t)) \quad (2)$$

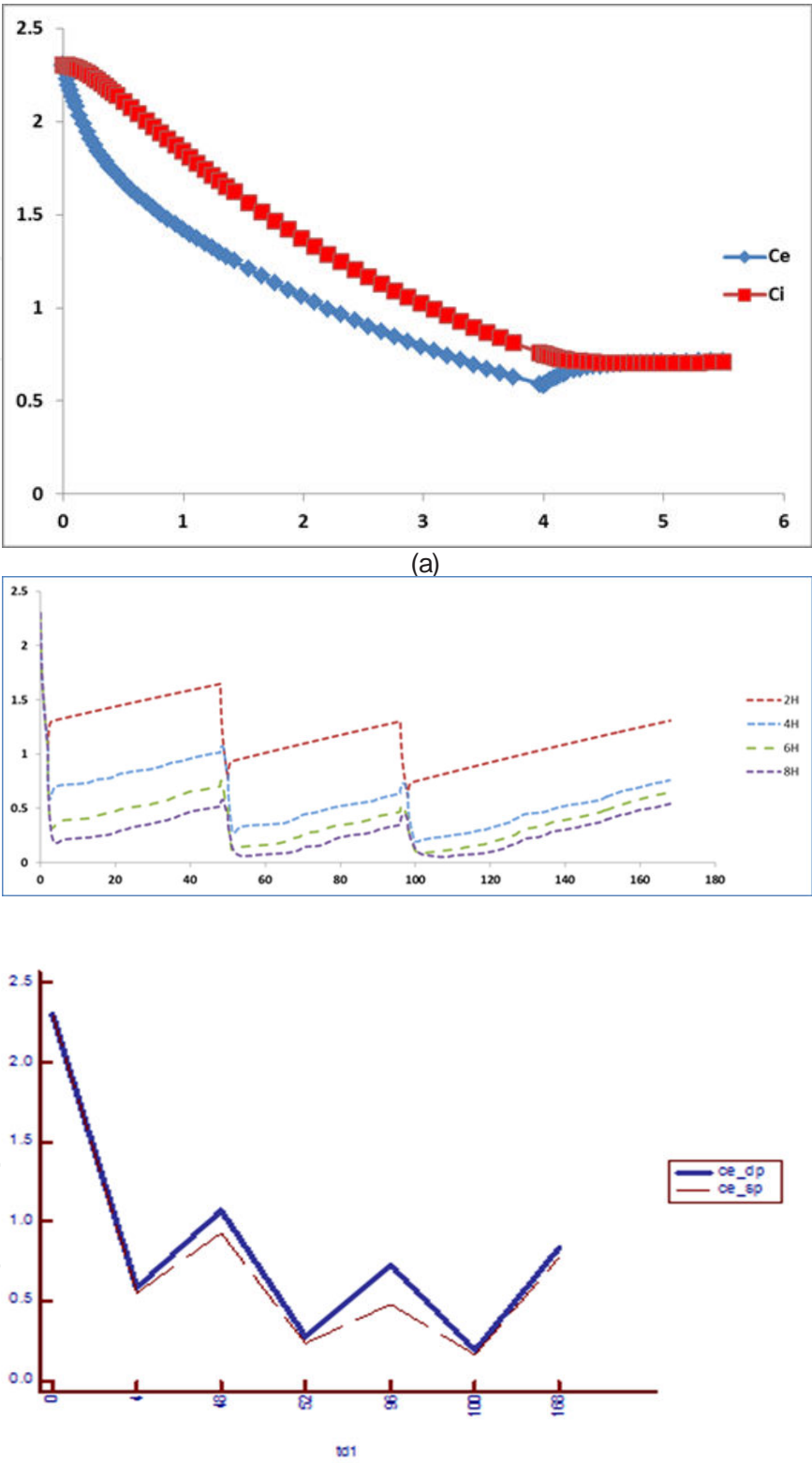
$$\frac{dV}{dt}(t) = \alpha(t) \quad (3)$$



**Figure 1.** Scheme of Variable-Volume Double Compartment dialysis kinetic model

Whereas “ $V$ ” is: solute distribution volume, “ $C$ ”: solute concentration, “ $K$ ”: clearance constant, “ $G$ ”: solute generation, “ $c$ ”: cellular, “ $e$ ”: extracellular, “ $i$ ”: intracellular, “ $r$ ”: renal, “ $d$ ”: dialyser,  $\alpha$ : volume change velocity (this constant is positive between dialysis sessions and negative during them), “ $t$ ”: time. Equations 1, 2 and 3 make a dependent differential equation system that can be numerically solved. Through these simulations, it is possible to obtain the time profile of intra and extracellular volumes and concentrations of the studied solutes (figure 2).

By defining a behaviour determined for several time intervals on certain variables, such as  $\alpha$  and  $K_d$ , it is possible to simulate different dialysis schedules, regarding session duration times (TD) and time between dialysis sessions or dialysis frequency (Fr).



**Figure 2.** (a) Simulation of a profile during HD and the rebound of the solute immediately after the end. (b) Simulation of the weekly HD profile showing the effect of increasing the TD with fixed  $K_d$  and  $K_c$ . (c) Urea dynamics simulated with double or single pool.

2.2. Simulated systems

2.2.1. Comparison between the true eq Kt/V and all the developed predictors

The simulations assumed that the subjects had a solute distribution volume of 580 ml/Kg and the intra and extracellular distribution relation is 2/3 and 1/3 of the total V. The extra-renal clearance constant (Ker) was considered invalid for the U.

Residual renal clearance (Kr) was 0. 1ml/min in all the cases.

Dialysis schedules with a duration between 2 and 8 hours at 2-hour-intervals of 2 hour were simulated and the weekly frequency of treatment were 3 and 7 days/wk.

The simulations resulted in a time-dependent evolution of the molecule concentration under study (U) in each of the compartments, that is, the intracellular (Ci) and extracellular (Ce) compartments.

We analysed 1005 determinations of U pre HD, U posHD and eqU (60 minutes after the end of the simulated session). This determinations were obtained in the midweek of the 4th and 10th week of simulation

These determinations were product of the manipulation of six (6) variables-Table 1-

Weight	Kc(ml/min)	Kd(ml/min)	U <sub>onset</sub> (mg%)	UF(ml/session)	UR%
60-120	400-1000	100-250	160 -240	500-4000	3.65-17.8

Table 1. Range of values of the different simulated variables.

U G was 6. 25mg/min in all the simulations.

2.2.2. Formulas

Simulated eqKt/V was compared with the previously described predictors with the next formulas :

$$Kt / V = Ln \left( \frac{U_{pos}}{U_{pre}} \right) \tag{4}$$

$$Kt / V = Ln \left( \frac{U_{eq}}{U_{pre}} \right) \tag{5}$$

$$Kt / V_{TATTERSALL} = Kt / V * \left[ \frac{t}{t + 35} \right] \tag{6}$$

$$Kt / V_{DAUGIRDAS} = Kt / V - 0.6 * \frac{Kt / V}{t} + 0.03 \quad (7)$$

$$Kt / V_{HEMO} = Kt / V - 0.39 * \frac{Kt / V}{t} \quad (8)$$

$$Kt / V_{LEYPOLDT1} = 0.924 * Kt / V - 0.395 * \frac{Kt / V}{t} + 0.056 \quad (9)$$

$$Kt / V_{LEYPOLDT2} = 0.915 * Kt / V - 0.485 * \frac{Kt / V}{t} + 0.106 \quad (10)$$

### 2.3. Changes in Kt/V, EKR and stdKt/V related to changes in TD and Fr

Typical 80-kg-patient with a residual renal clearance (Kr) of 0.1 ml/min and a weight gain a (interdialysis) and ultrafiltration (intradialysis) of 0.65 ml/min was chosen to simulate the different therapeutic dialysis schedules.

The assumption was that this typical patient would have a solute distribution volume of 580 ml/Kg (46.4 litres) and when the solute is U, the intra and extracellular distribution relation is 2/3 and 1/3 of the total V. The extrarenal clearance constant (Ker) was considered invalid for the U.

Dialysis schedules with a duration between 1 and 8 hours at intervals of 1 hour were simulated and the weekly frequency of treatment was changed from 3 to 7 days a week on each of them thus obtaining 28 different schemes.

The Fr applied to the simulations does not represent sessions uniformly distributed through the week; it was implemented according to the time tables used in the usual HD practice. For the 3-times/wk Fr, three sessions with an interval between the beginning of sessions of 48, 48 and 72 hours (that is, Monday, Wednesday and Friday) were performed. For the 4-times/wk sessions, the intervals are 24, 48, 24 and 72 hours. For the 5- and 6-times/wk sessions, 4 and 5 intervals of 24 hours and the last one of 72 and 48 hours, respectively, are established. When the Fr is of 7-times/wk, the distribution is uniform.

The simulations resulted in a time-dependent evolution of the molecule concentration under study (Urea) in the intracellular (Ci) and extracellular (Ce) compartments.

Over the U time profiles, the real Time Average Concentration (TAC) is calculated. Since the main objective was to evaluate which of the proposed indexes more accurately showed the dose changes caused by the scheme changes, the behaviour of the weekly Kt/V, EKR (Casino), std Kt/V (Gotch) and the rebound percentage (% rebound), were compared according to the following formulas:



$$\frac{Kt}{V} = \sum_{j=1}^N \ln \left( \frac{C_{ePre}}{C_{ePost}} \right)_j \quad (11)$$

$$TAC = \frac{1}{2N} \sum_{j=1}^N (C_{ePre} + C_{ePost})_j \quad (12)$$

$$EKR = \frac{G}{TAC} \quad (13)$$

$$std \frac{Kt}{V} = \frac{G}{\frac{1}{N} \sum_{j=1}^N (C_{ePre})_j} \quad (14)$$

$$\%R = \frac{100}{N} \sum_{j=1}^N \left( \frac{C_{eq} - C_{ePost}}{C_{eq}} \right)_j \quad (15)$$

#### 2.4. Hemodialysis simulation tool: HD-SIM

The simulations of hemodialysis kinetics were performed through the utilization of a software specially developed for hemodialysis simulation: HD-SIM. [15] This software was developed on MATLAB (c) platform and consists of a calculation core and a graphical user interface (GUI).

HD-SIM calculation core utilizes MATLAB ® (version 6. 5) simulation package SIMULINK® to support the VVDC kinetics model. Given the set of required parameters through the GUI, solute compartmental concentrations ( $C_e$  and  $C_i$ ) and volumes ( $V_e$  and  $V_i$ ) are calculated as functions of time. Concentration-time profiles are used for the calculation of different hemodialysis quantity-quality estimators such as: TAC, EKR,  $Kt/V$ , and  $stdKt/V$ . The calculation core solver is used with: ode113 algorithm (Adams – variable step) that is recommended by MathWorks for narrow tolerances, automatic integration step, maximum step of 1 (1 hr), duration of 1680 (10 weeks), absolute tolerance of  $10^{-7}$  ( $10^{-7}$  mg/ml) and relative tolerance of  $10^{-7}$ .

HD-SIM GUI provides a friendly set of windows that allows inserting patient and dialyzer specific data into the simulation system that is required to feed the VVDC model, defining sets of TDs and Frs to evaluate a wide range of treatment schedules, and managing the outcome of the simulations from visualizing estimator values and concentration profiles to file-saving selected results. (figures 3, 4 and 5)

HD-SIM - Datos del paciente

Ce0 [mg/mL]:	2.3
Cl0 [mg/mL]:	2.3
G [mg/h]:	375
Kr [mL/h]:	6
Ker [mL/h]:	0
KC [mL/h]:	36000
Peso [kg]:	80
UF [mL/periodo]:	6496
Relación V/P [mL/kg]:	580
Relación Vi/Ve:	2

OK Cancel

Figure 3. Patient and simulation data displayed by HD-SIM

HD-SIM - Datos de simulación

TDs [h]:	1 8
Fr [d/periodo]:	3 7
Periodo [h]	168
T0 [h]:	0
Tiempo de simulación [h]	1680
Inicio-Fin Transitorio [h]	0 168
Inicio-Fin Estacionario [h]	1512 1680

OK Cancel

Figure 4. Patient and simulation data displayed by HD-SIM

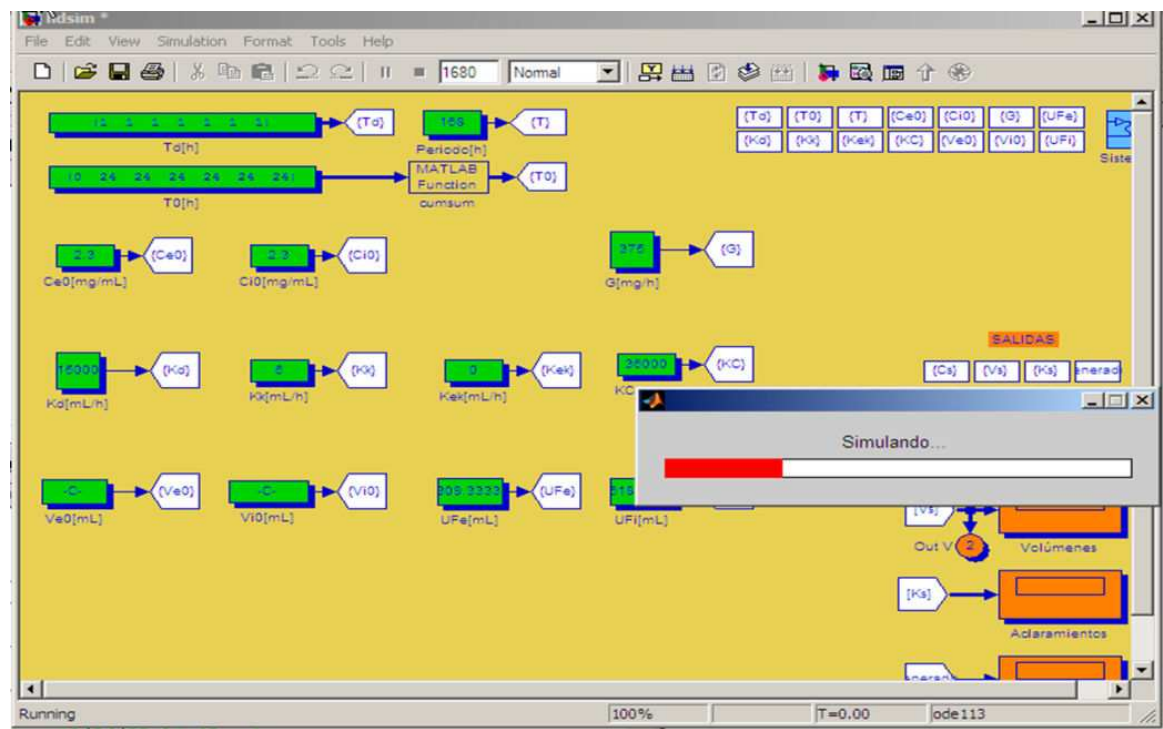


Figure 5. HDSIM running the simulations.

Table 2 shows the values at the the beginning of the simulation.

Solute	Ce onset (mg %)	G (mg/min)	Kc(ml/min)	Kd(ml/min)
Urea	230	6.25	600	250

Table 2. Values at the beginning of the simulation

### 3. Statistical analysis

All values are expressed as mean±standard deviation (sd) or median (range) as appropriate. Correlation coefficients were determined using the Pearson method. For analysis of agreement between methods (for example simulated (sim) eqKtV versus EqKtV predictors) we used Bland Altman analysis. To compare sim eqKtV with predictors we also used analysis of error: mean error (sim eqKtV-predictor) and % mean error ( (sim eqKtV-predictor)/ sim eqKtV) × 100). We used MedCalc version 12. 3. 0(MedCalc Software,Mariakerke,Belgium) for the statistical analysis.

## 4. Results

### 4.1. Prediction of the eqKt/V

The eq KtV delivered in 1005 simulations was  $0.84 \pm 0.47$  with a median of 0.78 and a range between 0.10 and 2.54, which represent the wide range of values commonly seen in current clinical practice. (Table 3)

	eqKt/V	Tattersall	Daugirdas	HEMO	Leypoldt 1	Leypoldt 2
Minimum	0.10	0.13	0.14	0.13	0.18	0.13
1st Quart	0.47	0.50	0.50	0.51	0.52	0.46
Mean	0.85	0.87	0.88	0.89	0.87	0.80
Median	0.78	0.80	0.82	0.82	0.81	0.75

**Table 3.** Statistical summary of Simulated and predicted eqKt/V values by different formulas. (1<sup>st</sup> Quart=first quartile)

### 4.2. Behaviour of predictors

All predictors showed a high Pearson correlation coefficient ( $\geq 0.99$ ) with sim eqKt/V and among themselves.

Daugirdas, Tattersall, HEMO and Leypoldt1 underestimated sim eqKt/V. Leypoldt2 was the only one to overestimate the sim eqKtV. (Tables 4 and 5)

	Daugirdas	Tattersall	HEMO	Leypoldt1	Leypoldt2
Mean	-0.0302	-0.0199	-0.0435	-0.0244	0.0428
SD	0.03680	0.03255	0.02959	0.05039	0.05670
Median	-0.0350	-0.0241	-0.0459	-0.0300	0.0304
Minimum	-0.101	-0.0836	-0.110	-0.110	-0.0454
Maximum	0.0783	0.0827	0.0721	0.170	0.259

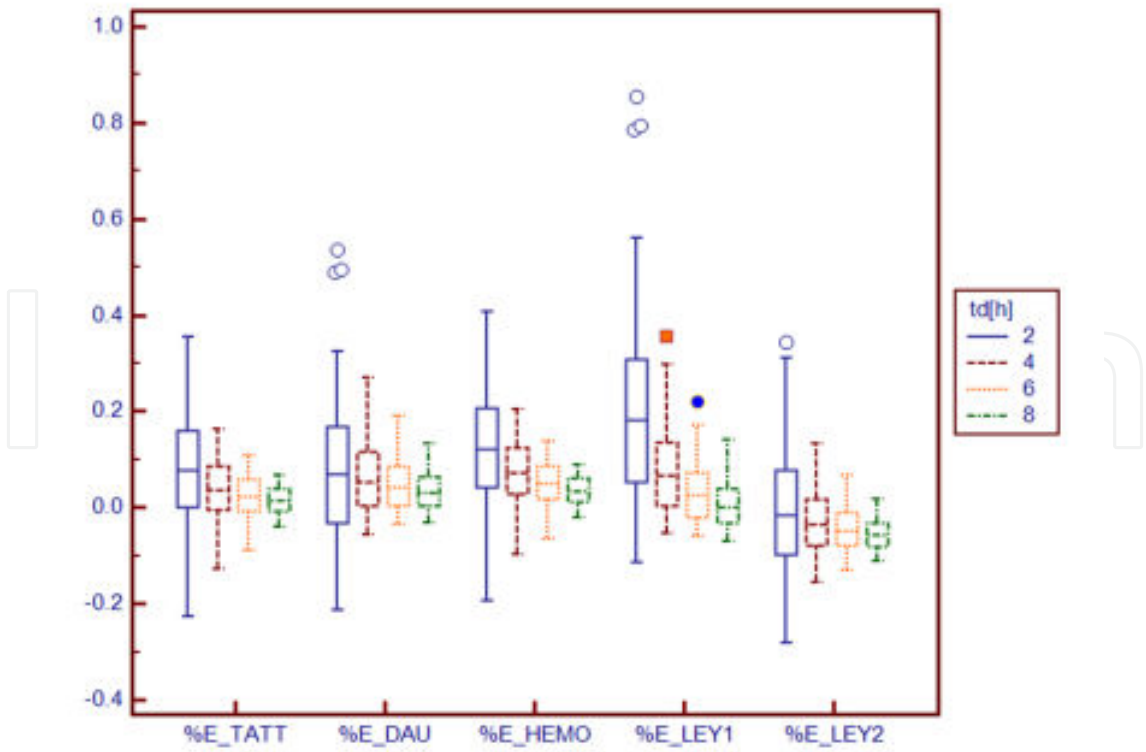
**Table 4.** Mean Error (ME) between sim eqKt/V and predictors

	Daugirdas	Tattersall	HEMO	Leypoldt1	Leypoldt2
Mean	5.63	4.32	7.47	7.63	-3.18
SD	7.7	6.9	7.42	11.83	6.67
Median	4.65	3.23	5.89	4.60	-3.9
Minimum	-2.14	-2.26	-1.95	-1.14	-2.82
Maximum	5.37	3.54	4.08	8.55	3.43

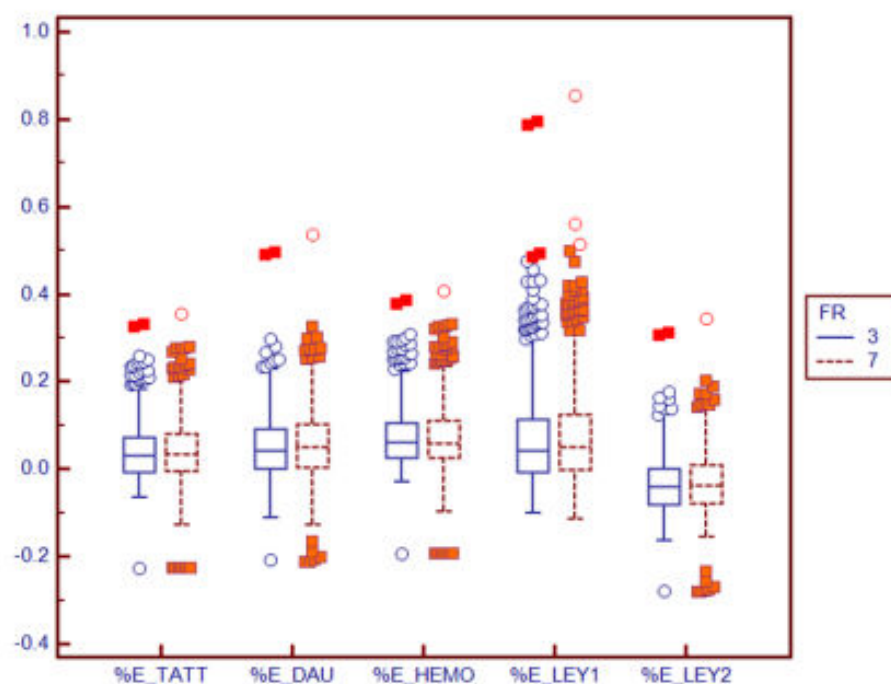
**Table 5.** % Error (% ME) between sim eqKt/V and predictors

The lower error of prediction expressed as ME or % ME was obtained with the Tattersall and the Daugirdas formula. Leypoldt1 and 2 showed the worst predictive performance.

One interesting point was the effect of increase TD of Fr it was used in unconventional schedules (different from 3-times/wk). Error was higher in schemes shorter than 4 hours and the increasing of Fr did not affect the prediction (Figures 6 and 7)



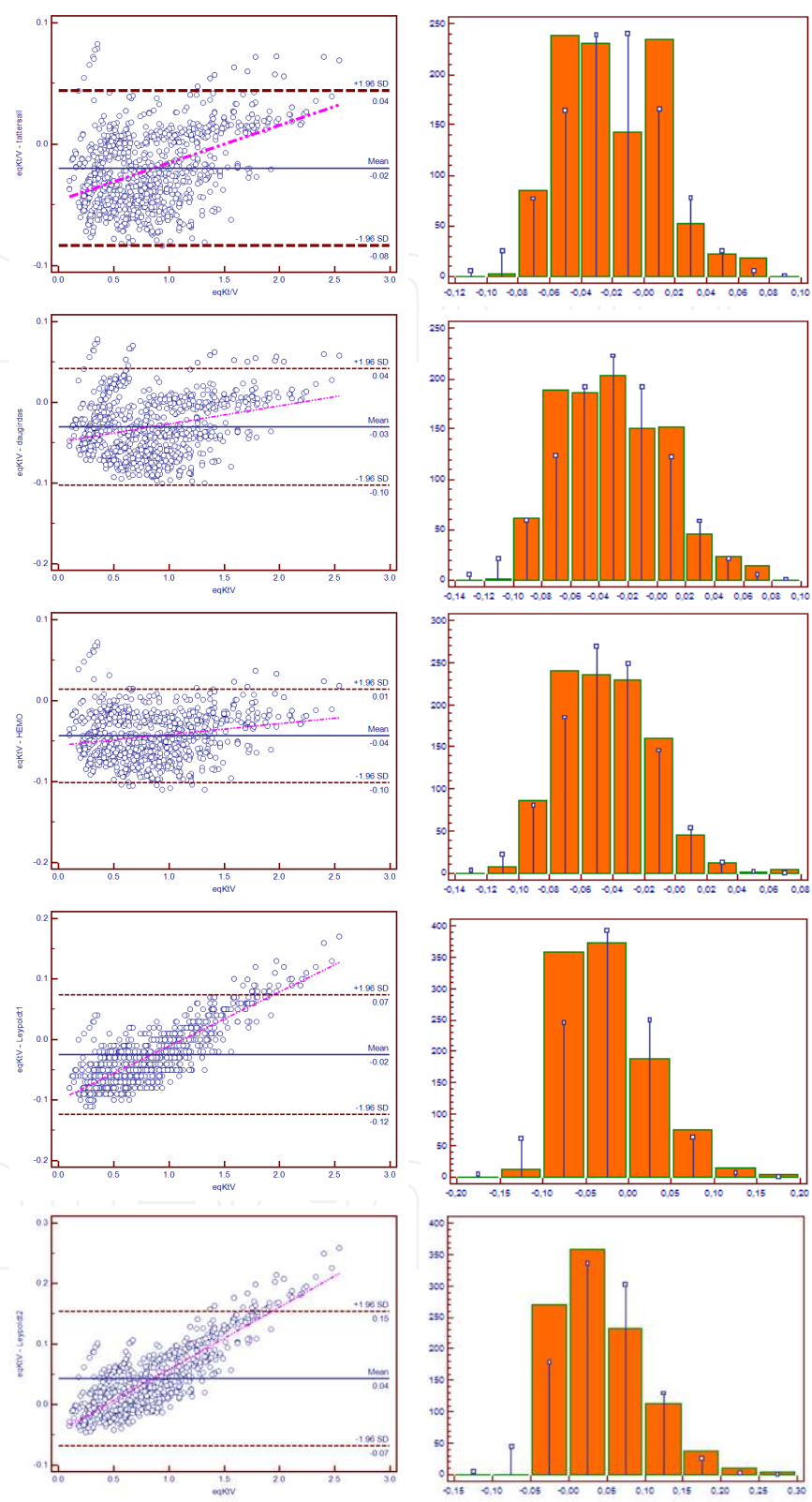
**Figure 6.** Effect of the TD and increased Fr in the % error prediction of eqKt/V



**Figure 7.** Effect of the TD and increased Fr in the % error prediction of eqKt/V

### 4.3. Bland-Altman analysis

A Bland-Altman analysis of agreement between gold standard (sim KtV) and eqKt/V predictors was performed. Tattersall and Daugirdas formulas showed the lower mean difference ( $\pm 2sd$ ): -0.02 (+0.04 -0.08) and -0.03 (+0.04 -0.1) respectively with a Gaussian distribution of error. Both Leypoldt formulas showed higher error with the increasing of the magnitude of eqKtV. HEMO study formula showed a higher mean difference than Tattersall and Daugirdas formulas with a lower 95% agreement interval (+0.01-0.1) (figure 8)



**Figure 8.** Left side: Bland Altman plot comparing simulated  $eq\ Kt/V$  and predicted  $eq\ Kt/V$  by different predictors formulae. Right side: Histogram of Error between simulated  $eq\ Kt/V$  and predicted  $eq\ Kt/V$  by different predictors formulae.

4.4. Quantification of the Weekly Dialysis Dose (WDD)

The minimal dialysis dose recommended by the DOQI standards ( $Kt/V$  U/session = 1. 2) corresponded to EKR U =3. 17 ml/min and stdKt/V U = 2. 07 ml/min in a usual scheme of 3 days/4 hours (3d4hs) and the high dose equivalent similar to HEMO study ( $EqKt/V=1. 4$ ) was 4. 28 ml/min and 2. 57 ml/min for stdKt/V in a schedule of 3 days 6 hours. Figure 9 shows the stdKt/V behaviour related to increase of TD and Fr as well as the equivalent values of minimal and high  $Kt/V$ .

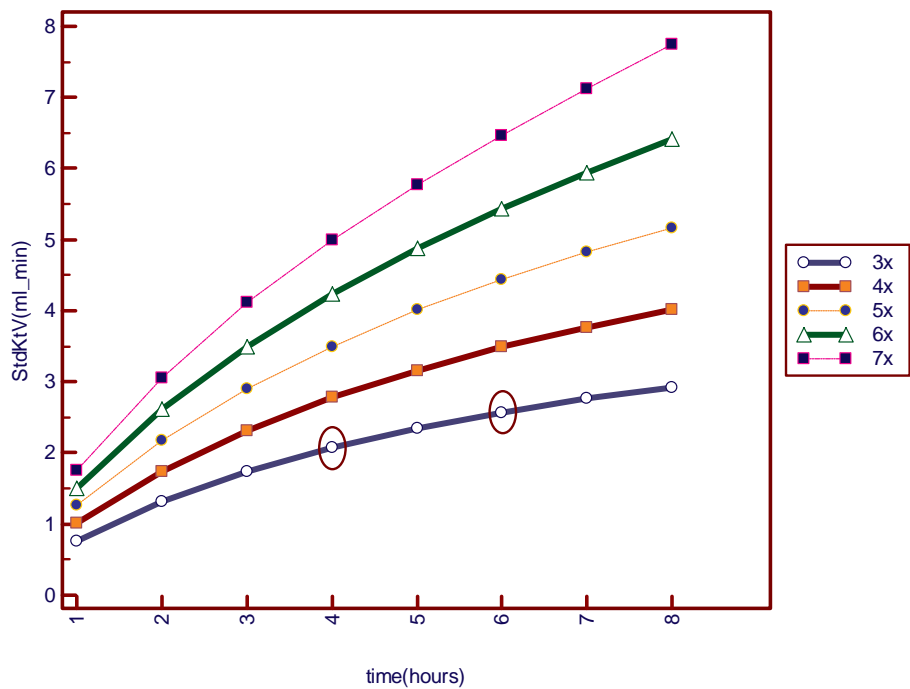


Figure 9. stdKt/V behaviour related to increase of TD and Fr as well as the equivalent values of minimal and high  $Kt/V$ .

Table 6 shows typical values of EKR, stdKt/V, wk  $Kt/V$  (weekly  $Kt/V$ ) and  $Kt/V$  by session according changes in TD y Fr in a typical 80-kg-patient.

Frequency	time[h]	EKR (ml/min)	stdKt/V(ml/min)	wk $Kt/V$ (ml/min)	KTV/Session
3	4	3.17	2.07	3.55	1.18
3	8	5.11	2.92	5.82	1.94
4	4	4.23	2.78	4.61	1.15
7	2	4.06	3.05	4.78	0.68
7	4	7.45	5	7.52	1.07
7	8	12.69	7.75	10.54	1.51

Table 6. EKR, stdKt/V, wkKt/V and Kt/V by session according changes in TD and Fr in a typical 80-kg-patient. (Ce onset=230;KD=250 ml/min;Kc=600ml/min.



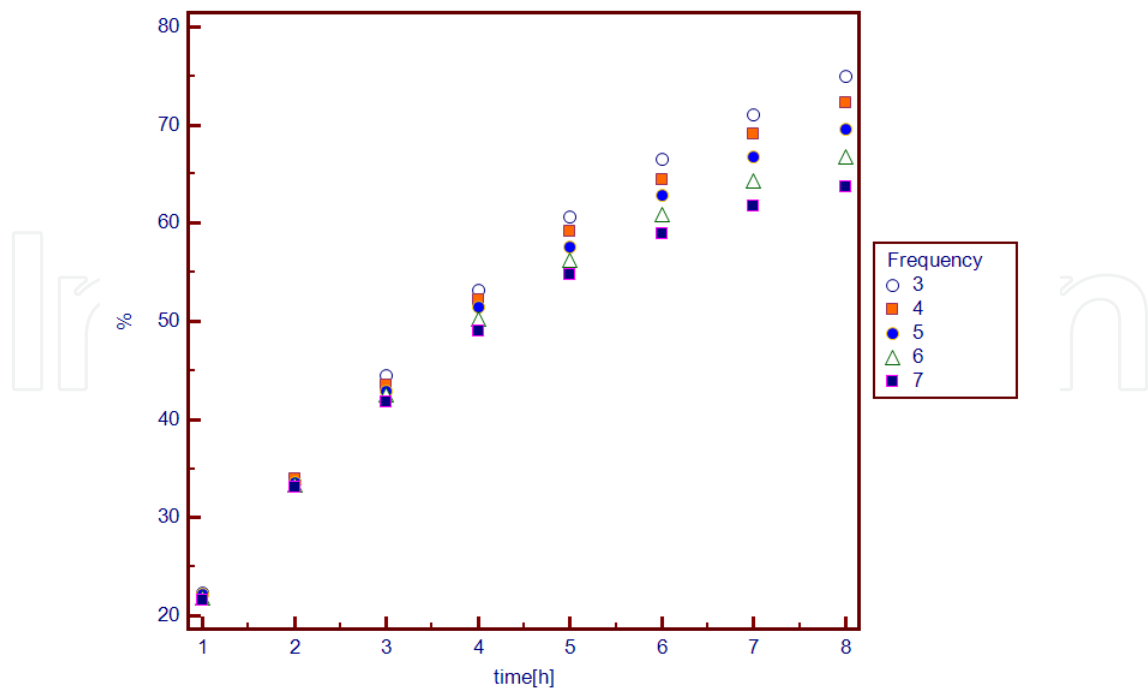
The weekly Kt/V, EKR and std Kt/V showed a high correlation to express increasing of TD and Fr (weekly Kt/v-std Kt/V  $r=0.987$  EKR-stdKt/V  $r=0.9937$ ) showing the weekly Kt/V ( $5.68\pm2.46$ ) and the EKR ( $5.55\pm3.02$ ) values to be higher than std Kt/V ( $3.56\pm1.76$ )

The behaviour proved different when the three indexes were separately analysed. When they are compared to quantify 3-times/wk and weekly schedules, the ekr and std Kt/V have a similar behaviour, the EKR tending to overestimate the WDD as the TD increases. (Figure 11) When the difference EKR-std Kt/V is showed in a graph (Figure 10) a high correlation of it ( $R^2=0.99$ ) is verified, with a logarithmic increase of the Kt/V/session and is lower with the increase of Fr in a fixed TD. The weekly Kt/V has a behaviour similar to that of the EKR in the 3-times/wk schedules but clearly fails in the daily schedules, especially in the TD schedules >4 hours.

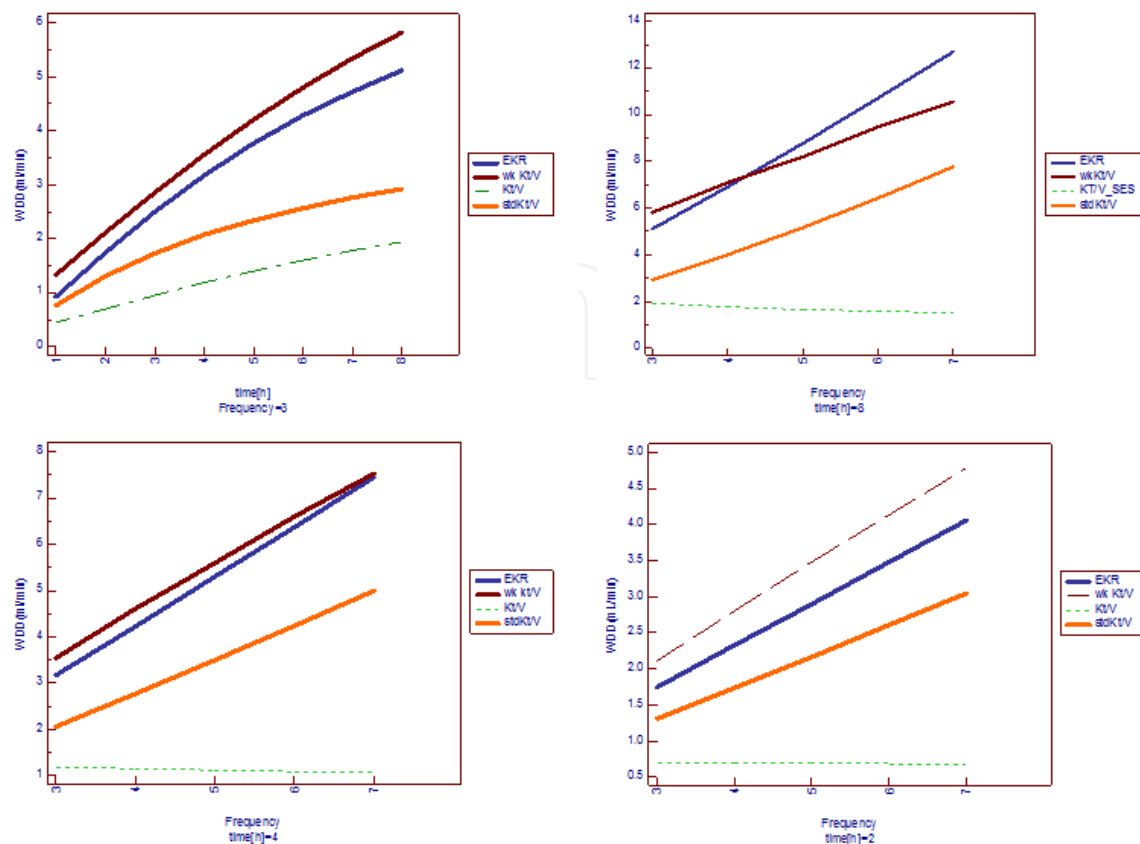
When the Kt/V-session is analysed, the results match. The Kt/V/session increases as the TD increases when a certain number of sessions are fixed (Fr). When it is analysed for different Frs, the Kt/V/session only shows differences when duration is > 4 hours; however, if the Fr varies and the TD is fixed, instead we can observe that the Kt/V/session is not able to respond to the dose increases and tends to decrease as the WDD increases due to an increment of the Fr. (Figure 11)

The U rebound is complete one hour after the end of the HD session in all the simulations, decreasing as the TD increases.

Figure 11 showed the effect of TD and Fr on different predictors of the WDD (wkKt/V, EKR and stdKt/V) as well the changes Kt/V-session.



**Figure 10.** Difference (%) EKR-stdKtV related to Kt/V by session



**Figure 11.** Effect of changes in increasing of TD and Fr on the behavior of WDD predictors (wkKt/V, stdKt/V, EKR) and Kt/V by session. (WDD=Weekly Dialysis Dose (ml/min))

#### 4.5. Comparison of V with BSA to normalize Kt/V

In the last four decades dialysis dose expressed as Kt/V has been widely used due to its low complexity and ability to predict to be a strong predictor of mortality in HD population. However, recent studies showed paradoxical outcomes related to sex and higher mortality in patients with high Kt/V and low Volume, leading to the proposal of a normalized volume using and the correction by a Volumen normalized by Body Surface Area (BSA). has been proposed. [16]

We randomly simulated 1031 K\*t with a range of between 14400 ml/min and 57600 ml/min and then Kt/V (using Watson formula for Volume) and Kt/V corrected by BSA (Dubois formula) were calculated and analysed

KtV values delivered by simulation showed a mean of 1.01, a median of 0.99, a range between 0.29-2.44 and a standard deviation of 0.40 The results of the allometrical correction of Volume Watson formula by BSA were  $0.084 \cdot V^{0.86}$  (female)  $r=0.98$  and  $0.1229 \cdot V^{0.73}$  (male)  $r=0.99$ . (Figure 12)

The results after V normalized by BSA clearly changed between men and women and the overestimation in patients with lower volumes was corrected (Table 7 and figures 13 and 14)

	Sex			
	f		m	
	Mean	SD	Mean	SD
Kt/V	1.158	0.4354	0.921	0.3415
Kt/Vcorr	1.862	0.6891	2.489	0.8909

Table 7. Kt/V and Kt/V corrected by BSA (Dubois) according to sex.

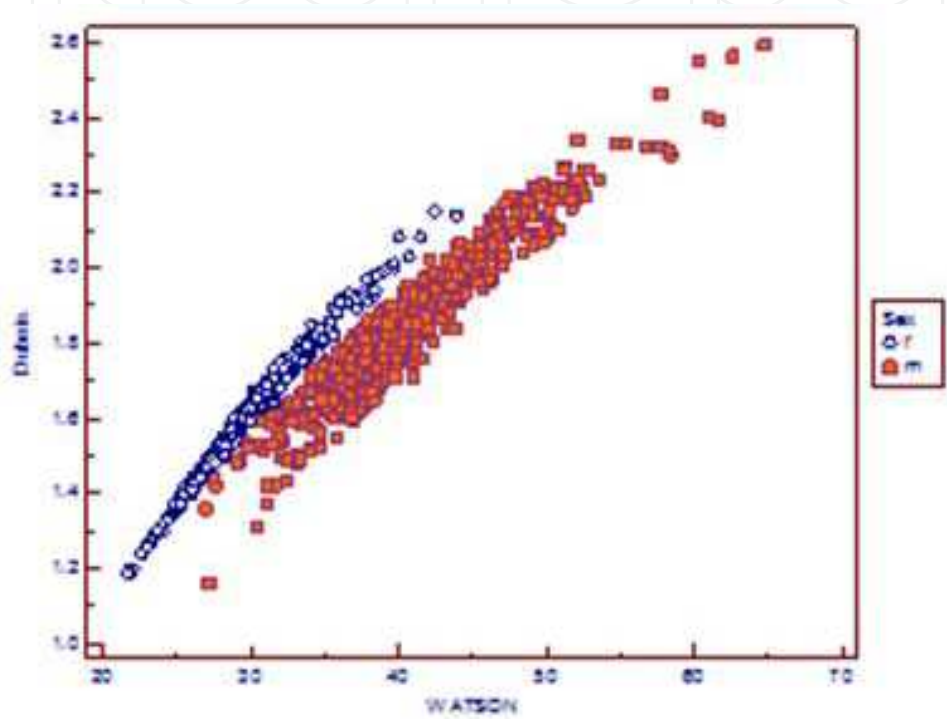


Figure 12. Allometric regression between Body Surface Area (Dubois) and Volume (Watson)

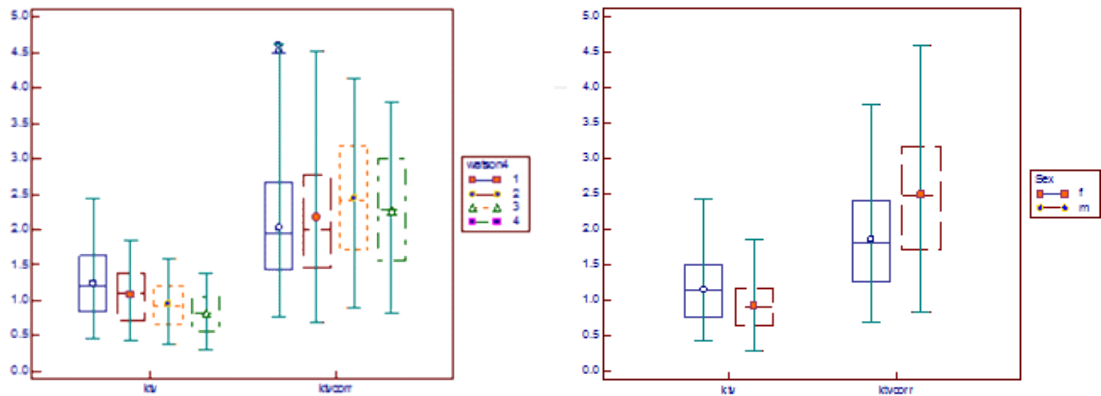


Figure 13. Effect of changes in Volume and Sex on BSA-normalized Kt/V and Watson Kt/V

## 5. Discussion

In this work we propose the simulation with a VVDC kinetic model as a useful and safe tool to investigate, learn and find out the numerous aspects of the HD treatment related to dialysis dose. Single pool models used by Gotch [10] to developed the pharmacokinetic concept of  $Kt/V$  are simpler and also useful but it frequently leads to errors in showing the true behaviour of little known molecules or not yet validated treatments. VVDC kinetic model is used in current studies that analyze the influence of increasing TD and Fr in HD outcomes after the failure of HEMO study to demonstrate better results with high dose expressed as  $eqKtV$ . [2]

Exponential decay curves defined by WWDC to fit dialysis dose by session are actually used in several medical devices based on ionic dialysance or urea sensors. [17] [18]

We used WWDC based curve fitting and neural networks to predict dialysis dose from samples provided by an on-line urea monitor. [17]

The main interpretation of the double compartment [19] represent intra and extracellular fluid spaces, with diffusion of molecules between the spaces characterised by a mass transfer coefficient,  $K_c$ . This interpretation is based on the observation that  $K_c$  correlated with patient size. This model had been deeply developed by Smye and it had been the basis of the Tattersall formula. However, Scheneditz et al suggests that the two compartment based in different regional tissue flows (high and low blood flow) may describe urea distribution, and transport during dialysis, more accurately. This theoretical approach also permitted the development of a formula for dialysis dose that accounts for molecular rebound but only is based only on measurements of urea made during HD procedure. This formula has proved higher clinical usefulness: the Daugirdas formula.

In this study we confirmed the robustness of the two widespread  $eqKtV$  predictors developed under the two different ways: Tattersall [7] and Daugirdas formulas. They showed a high accuracy in the numerous simulated schedules. The lower error of Tattersall formula has been validated in clinical situations and could be explained in our study because it was developed under a theoretical approach using a diffusion-based VVDC.

Formula emerged from the blood U samples analysis of 1131 patients in the HEMO study [8] showed as an interesting approach. It behaved with a higher error than Tattersall and Daugirdas formulas but showing a very low bias in all the simulations.

$Eq KtV$  was confirmed as the metric of dialysis session in the thrice a week schedule. Equivalent dose of  $stdKt/V$  for  $eqKt/V$  in schedules  $>3$ -times/wk may be easily calculated in a graphical fashion (Figure 9)

The main issue which justifies the fact that  $Kt/V$  U is considered the key of the adequacy of dialysis is that it is related to mortality. However, many studies have questioned the utility of  $Kt/V$ : mainly, scaling for the volume is a confounding factor since gender and body mass index directly affect morbidity and mortality in HD patients. [20]

In our study the influence of the denominator to achieve a real dose independent of sex and volume showed similar results with others studies.

VVDC proved particularly useful when we analysed the new proposed predictors of the WDD: EKR and standard Kt/V.

Std KtV was confirmed as the best project to explain the different schedules. EKR was showed closely related with Kt/V and sensitive to changes in TD, overestimating the dose in daily HD schedules. VVDC allowed to graph different weight, dialyzer and patient clearances, etc.

Other molecules such as B2M [21] and phosphorus related to mortality and different behaviour with urea have not been simulated in this work but VVDC have been successfully used for both. B2M is a molecule of high molecular weight, with typical lower levels in plasma and lower distribution Volume fully explained by VVDC when we know completely their characteristics. On the contrary, Phosphorus [22] shows a heterogeneous and complex behaviour that cannot be completely validated with a VVDC kinetic model.

In addition to U kinetics, clinicians must consider clinical indicators (in example extracellular volume control, blood pressure, anemia and cardiovascular status) and comorbidities (diabetes, ageing, undernutrition) when using frequent or prolonged dialysis no forgetting to provide the best possible clinical results and quality of life.

## 6. Conclusions

In our experience, a VVDC kinetic model proved to be showed as a useful and safe tool to analyse different HD schedules and novels techniques before the clinical validation. The use of graphical interfaces to extrapolate the numerical results enhanced the VVDC simulation. Clinical practice and simulation interact in a permanent feedback. Std KtV was confirmed as the best project to explain the different schedules. Tattersall and Daugirdas showed highly accurate in the numerous simulated schedules.

## Author details

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