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A Model to Predict Optimal Dialysate Flow

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Abstract: Diffusive clearance depends on blood (Qb) and dialysate flow (Qd) rates and the overall mass transfer area coefficient (KoA) of the dialyzer. In this article we describe a model to predict an appropriated AutoFlow (AF) factor (AF factor = Ratio Qd/Qb), that is able to provide adequate Kt/V for hemodialysis patients (HDP), while consuming lower amounts of dialysate, water and energy during the treatment. We studied in vivo the effects of three various Qd on the delivered dose of dialysis in 33 stable HDP. Hemodialysis was performed at Qd of 700 mL/mn, 500 mL/mn, and with AF, whereas specific dialysis prescriptions (treatment time, blood flow rate [Qb], and type and size of dialyzer) were kept constant. The results showed that increasing the dialysate flow rate more than the model of AF predicted had a small effect on the delivered dose of dialysis. The Kt/V (mean ± SD) was 1.52 ± 0.16 at Qd 700, 1.50 ± 0.16 at Qd 500, and 1.49 ± 0.15 with AF. The use of the AF function leads to a significant saving of dialysate fluid. The model predicts the appropriate AF factor that automatically adjusts the dialysate flow rate according to the effective blood flow rate of the patient to achieve an appreciable increase in dialysis dose at the lowest additional cost. **Key Words:** AutoFlow factor, Clearance, Dialysate economy, Dialysate flow, Michaels equation.

The delivered dose of dialysis is an important predictor of patient outcome (1,2). In the National Kidney Foundation Dialysis Outcomes Quality Initiative (DOQI) Clinical Practice Guidelines for Hemodialysis (HD) Adequacy, a minimum urea equilibrated Kt/V (eKt/V) of 1.2 is recommended for three dialysis sessions per week and in the absence of residual renal function (3).

Accurate prediction of dialyzer urea clearance during hemodialysis is essential when prescribing therapy using urea kinetic modelling. The delivered dose of dialysis depends on the flow conditions (blood, dialysate and ultrafiltration flow), dialysis time and the product of the overall mass transfer coefficient and membrane surface area (KoA) (4,5).

Since the 1960s, the dialysate flow rate (Qd) has routinely been maintained at 500 mL/min because this value was chosen as optimum in Kiil dialyzers (6,7). Recent studies have showen that for dialyzers with features that promote good dialysate flow distribution, increasing Qd excessively beyond this is likely to have only a modest impact on dialyzer performance (8).

In the current climate of constant economic restraints, the novel AutoFlow (AF) function of some dialysis machines, such the 5008 Therapy System (Fresenius Medical Care, Bad Homburg, Germany), adjusts Qd automatically according to the effective blood flow rate (Qb) of the individual patient at a selected AutoFlow factor (Qd = AF factor × Qb). The consequence of this approach is a significant saving in dialysis fluid consumption at the highest achievable clearance that can be reached at an appropriately selected AutoFlow factor (9).

In the present study we describe and evaluate a mathematical model to calculate an appropriate AutoFlow factor that determines the optimum Qd. The AF function of some dialysis machines is an example of applying this model.

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PATIENTS AND METHODS

Patients

In this prospective single-center study with crossover design performed at the Military Hospital of Instruction, Mohammed V, Rabat, Morocco, the in vivo effect of Qd on urea kinetics was examined in 33 maintenance hemodialysis patients (HDP) after obtaining informed consent. All patients had intact arteriovenous fistulas and underwent dialysis regularly thrice weekly. For inclusion in the study, subjects were required to be older than 18 years, stable clinically and hemodynamically, have a constant hemodialysis prescription, and an expected fluid removal of no more than 3 liters per treatment.

Modeling the appropriate AutoFlow factor

The model is based on the Michaels equation that predicts the theoretical urea clearance (K) (10,11):

$$K = \frac{1-\exp\left[\frac{KoA}{Qbw}\left(1-\frac{Qbw}{Qd}\right)\right]}{\frac{Qbw}{Qd}-\exp\left[\frac{KoA}{Qbw}\left(1-\frac{Qbw}{Qd}\right)\right]}\cdot Qbw\left(1-\frac{Qf}{Qbw}\right)+Qf \quad (1)$$

where K is the dialyzer urea clearance, Qd is dialysate flow rate (milliliters per minute), Qf is ultrafiltration rate, KoA is mass transfer area coefficient for urea (milliliters per minute), and Qbw is blood water flow (milliliters per minute):

$$Qbw = \alpha.Qb \text{ where } (\alpha = 0.94 - 0,0022 \cdot \text{Hematocrit}(\%)) \quad (2)$$

Equation 1 describes urea clearance (K) as a function of the dialyzer constant, KoA, and clinical flow rates and may be used to compute either K or KoA when either one is known. It was developed under the assumption of countercurrent flows. The mass transfer area coefficient, KoA, is the product of the overall mass transfer coefficient and the area of the diffusion front.

In response to variations in Qd, the maximum clearance K can be expressed as:

$$K.max = \lim_{Qd\to+\infty} K = \frac{1-\exp\left[\frac{KoA}{Qbw}\right]}{-\exp\left[\frac{KoA}{Qbw}\right]}\cdot Qbw\left(1-\frac{Qf}{Qbw}\right)+Qf \quad (3)$$

Combining Equation 3 with 1 yields:

$$\exp\left[\frac{KoA}{Qbw}\left(1-\frac{Qbw}{Qd}\right)\right] = \exp\left(\frac{KoA}{Qbw}\right)-\frac{Qbw}{Qd}\cdot\left[\exp\left(\frac{KoA}{Qbw}\right)-1\right] \quad (4)$$

Equation 4 reflects the conditions of variables (Qb, Qd and KoA) which allow the same urea clearance that observed with a maximum of dialysate flow.

Considering $\frac{Qbw}{Qd} = x$, Equation 4 becomes:

$$\frac{KoA}{Qbw}\cdot(1-x) = Ln\left[\exp\left(\frac{KoA}{Qbw}\right)-x\left(\exp\left(\frac{KoA}{Qbw}\right)-1\right)\right] \quad (5)$$

Derivation of Equation 5 in the case that variation of Qd is not associated with change of Qb and KoA, leads to:

$$-\frac{KoA}{Qbw} = \frac{-\left(\exp\left(\frac{KoA}{Qbw}\right)-1\right)}{\exp\left(\frac{KoA}{Qbw}\right)-x\left(\exp\left(\frac{KoA}{Qbw}\right)-1\right)}$$

Therefore we conclude that:

$$\frac{Qd}{Qbw} = \frac{1}{X} = \frac{\exp\left(\frac{KoA}{Qbw}-1\right)}{\left(1-\frac{Qbw}{KoA}\right)\cdot\exp\left(\frac{KoA}{Qbw}\right)+\frac{Qbw}{KoA}} \quad (6)$$

After substitution of Qbw by Qb (see Eq. 2) in Equation 6, the AutoFlow factor can be expressed as:

$$\text{AutoFlow factor} = \frac{Qd}{Qb} = \alpha\cdot\frac{\exp\left(\frac{KoA}{\alpha Qb}\right)-1}{\left(1-\frac{\alpha Qb}{KoA}\right)\cdot\exp\left(\frac{KoA}{\alpha Qb}\right)+\frac{\alpha Qb}{KoA}} \quad (7)$$

Or by this simplified formula if we consider that Qb was assumed to be the blood water flow rate Qbw. This simplified equation will lead to a small overestimation of the real AutoFlow factor.

$$\text{AutoFlow factor} = \frac{\exp\left(\frac{KoA}{Qb}\right)-1}{\left(1-\frac{Qb}{KoA}\right)\cdot\exp\left(\frac{KoA}{Qb}\right)+\frac{Qb}{KoA}} \quad (7\text{simplified})$$

This model predicts the appropriate AutoFlow factor according to KoA, Qb and hematocrit, to ensure optimal balance between clearance and dialysate consumption. The general predictions of the model are presented graphically in the Results section.

Study design

The purpose of this study was to keep the dialysis regimen constant during the study period except for varying Qd.

All patients were dialyzed with Fresenius 5008 dialysis machine for at least 3 consecutive weeks at each of the three Qd as follows:

- Week 1: three sessions with Qd at 500 mL/mn.
- Week 2: three sessions with appropriately calculated AutoFlow factor (From simplified Eq. 7).
- Week 3: three sessions with Qd at 700 mL/mn that ensure an AF factor > 2 in all patients.

The membranes used in the study were Polyamix (Polyflux H 140, 170, and 210; KoA = 993, 1145, and 1450 mL/min, respectively, Gambro, Lund, Sweden) with a surface area of 1.4, 1.7, and 2.1 m^2. Dialyzers, treatment time, anticoagulation and Qb were not changed during the study period. Care was taken to accurately deliver the prescribed dialysis time and the Qb. The technical data of the dialyzers used are listed in Table 1.

During the dialysis treatment the following parameters were acquired and recorded directly from the machine displays: effective blood flow rate, dialysate flow rate, ultrafiltration volume, cumulated blood volume, effective dialysis time, recirculation by blood temperature monitor (BTM), weights before and after dialysis, arterial and venous pressures of extracorporeal circuit. We noted that BTM temporarily increased the Qd to 800 mL/mn to measure recirculation. The 5008 system offered a function that allowed for either a manual or automatic compensation of the effective blood flow rate to that prescribed for the patient by means of a compensatory mechanism within the software of the system.

In this study we evaluated the impact of different flow rates of dialysis fluid on the dialysis efficacy:

1. Measured by conductivity monitoring using the OCM (Online Clearance Monitor, Fresenius Medical Care, Bad Homburg, Germany); Observed ionic dialysance (K.ocm) multiplied by the real duration of the session is used to calculate the Kt.ocm. To calculate the (KT/Vw.ocm), the urea distribution volume (Vw) was determined using the Watson formula taking into account post-dialysis weight, height, gender and age (12).
2. Calculated according to the Michaels equation after correction for recirculation (R): (Effective theoretical clearance; K.th) (13):

$$K.th = K\frac{(1-R)}{\left[1-R\cdot\left(1-\frac{K}{Qbw}\right)\right]}$$

Statistics

Comparative study was conducted using the Student's paired *t*-test and with the exact two-sided McNemar's test. Statistical significance was assumed for *P* less than 0.05.

RESULTS

Patients

A total of 16 women and 17 men with an average age of 49 ± 17 years were enrolled in the study. They had been receiving hemodialysis for 63 ± 53 months. Demographic data of the 33 patients are summarized in Table 2.

The model predicting the appropriate AutoFlow factor

The model shows that AF depends on the ratio KoA/Qb. The AF factor is theoretically between 1 and 2 (see Fig. 1). According to the KoA and Qb the AF was 1.3 in 75% of hemodialysis patients, and 1.4 in 25% of patients in our study.

TABLE 1. *Technical data on the dialyzers used*

	Polyflux 140H	Polyflux 170H	Polyflux 210H
Effective surface area (m^2)	1.4	1.7	2.1
Wall thickness of fiber (μm)	50	50	50
Inner diameter of fiber (μm)	215	215	215
Packing density (%)	45	45	45
KoA for Urea (mL/mn)	993	1145	1450
Effective length of hollow fiber (mm)	270	270	270
Hollow-fiber shape	Fibers with micro undulations		
Membrane components	Polyamix: Polyarylethersulfone, Polyvinylpyrrolidone and Polyamide blend		

TABLE 2. *Patient characteristics*

Male/female (*N* / *N*)	16/17
Age (years)	49 ± 17 (19 to 76)
Time on hemodialysis (months)	63 ± 53 (9 to 306)
Etiology of end-stage renal disease (%)	
Hypertension	6.1
Interstitial nephritis	15.1
Glomerulonephritis	6.1
Diabetes	9.1
Unknown	48.5
Polycystic kidney disease	6.1
Others	9
Hematocrit (%)	33.4 ± 4
Serum protein (g/L)	67 ± 6
Body mass index (kg/m^2)	24 ± 2

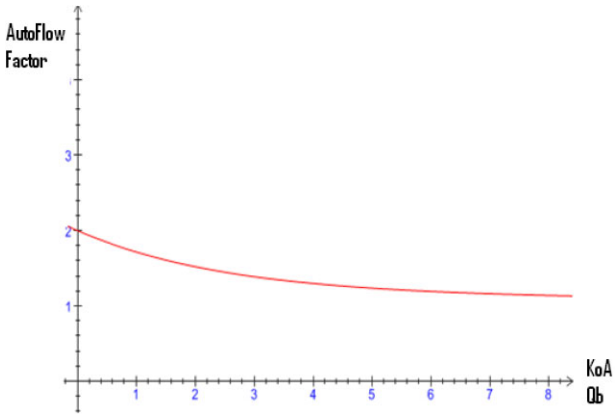

FIG. 1. Prediction of the appropriate AutoFlow (AF) factor from simplified Equation 7 according to the KoA and Qb. In this graph Qb was assumed to be the blood water flow rate. The AF factor depends on the ratio (KoA/Qb) and is theoretically between 1 and 2.

Dialysis treatment

297 dialysis sessions were evaluated. There were no changes in dialysis modalities or dialytic parameters except modification of Qd over the period of the study (see Table 3).

Mean dialysis dose both theoretical (K.th) and measured by ionic dialysance (Kocm) at each of three Qd is shown in Table 4 and Figure 2. The variation of delivered dose of dialysis among the three dialysate flow rates was modest: the mean dialysis dose by applying the AutoFlow factor (week 2), was 1.49 ± 0.15 Kt/V which is similar to that observed for conventional dialysate flow at 500 mL/mn (week 1: 1.50 ± 0.16 Kt/V), but it was slightly lower (less than 2%) to that found at high Qd (week 3; 1.52 ± 0.16 Kt/V). The proportion of patients with Kt/Vw.ocm more than 1.2 did not differ significantly between the dialysate flow rates.

Dialysate saving potential via the application of the AutoFlow function

Conventional dialysate flow rates of 500 mL/min utilized a total volume of about 120 L of dialysate (purified water, acid concentrate, bicarbonate) over a dialysis session. By coupling the dialysate flow rate to the effective blood flow rate through the application of the AutoFlow function of the 5008 Therapy System, an average saving of 20% of purified water, 20% of Acid concentrate and 23% of the half-life of bicarbonate powder was observed compared with standard HD treatments (see Table 5).

TABLE 3. *Characteristics of hemodialysis treatments at different dialysate flow rates*

	Dialysate flow rate (Qd)		
	Qd with AF	Qd 500	Qd 700 (AF > 2)
No. of measurements (*N*)	99	99	99
Dialysate flow rate (mL/min)	404 ± 29	500*	700″
Weight before dialysis (Kg)	63.5 ± 9	64 ± 9	63.5 ± 9
Weight after dialysis (Kg)	62 ± 9	62 ± 9	61.4 ± 9
Total ultrafiltration (mL)	1885 ± 923	1914 ± 854	1934 ± 843
Mean real blood flow (mL/min)	301 ± 26	300 ± 24	301 ± 25
Effective dialysis duration (min)	250 ± 14	251 ± 12	250 ± 28
Recirculation (%)	10.6 ± 2	11 ± 2	11 ± 4
Cumulated blood volume (L)	74.8 ± 9	74 ± 9	74 ± 8
Average arterial pressure† (mmHg)	–155 ± 31	–154 ± 30	–156 ± 28
Average venous pressure† (mmHg)	136 ± 23	132 ± 21	131 ± 22

*$P < 0.001$ for Qd of AutoFlow (AF) versus 500 mL/min, Student's paired two-tailed *t*-test. ″$P < 0.001$ for Qd of AF versus 700 mL/min, Student's paired two-tailed *t*-test. Values expressed as mean ± SD. Treatment regimen was kept constant during the study period, as shown by selected treatment parameters. †Arterial and venous pressures of extracorporeal circuit.

TABLE 4. *Comparison of dose of dialysis at different dialysate flow rates*

	Dialysate flow rate (Qd)		
	Qd with AF	Qd 500	Qd 700
K.th (mL/min)	221 ± 22	224 ± 20 NS	224 ± 24 NS
K.ocm (mL/min)	200 ± 18	202 ± 16 NS	205 ± 18*
Kt.ocm (L)	50.3 ± 6	50.8 ± 6 NS	51.3 ± 6*
Kt/Vw.ocm	1.49 ± 0.15	1.50 ± 0.16 NS	1.52 ± 0.16*
Patients with (Kt/Vw.ocm) > 1.2	100%	100% NS	100% NS

*Significant ($P < 0.05$). Comparison for Qd of AutoFlow (AF) versus 500 mL/min, and for Qd of AF versus 700 mL/min. NS, Not significant ($P > 0.05$).

DISCUSSION

Because the correlation between Kt/V as a marker of dialysis adequacy and patient mortality and morbidity has been established (14), efforts have been undertaken to optimize dialysis efficacy, particularly because some HD patients do not reach the eKt/V threshold of 1.2 recommended by the DOQI guidelines (3,15). Classic measures to improve Kt/V included alterations in treatment time or frequency, Qb, and/or dialyzer surface area. It is generally assumed that only small increments in urea clearance, and thus Kt/V, are obtained by increasing Qd (16). There is also consensus to suggest that much higher doses beyond 1.2 eKt/V are able to provide a significant additional benefit to the patient in terms of improved survival (17).

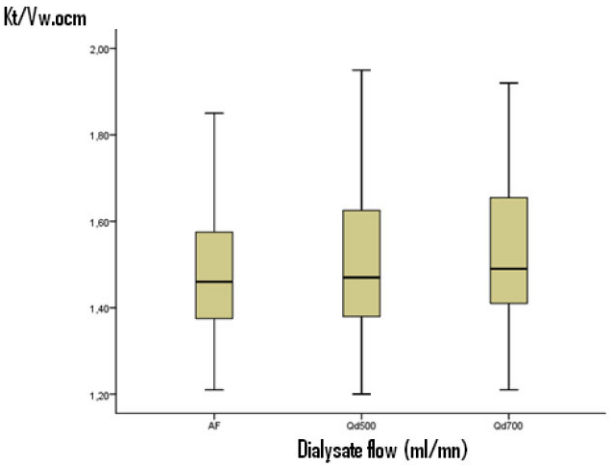

FIG. 2. Effect of three different Qds on Kt/V with appropriate AutoFlow (AF) factor. Qd700 ensures an AF factor greater than 2 in all patients. The figure shows a small effect of increasing dialysate flow rate more than AF, on delivered dose of dialysis.

In their report, Kult and Stapf showed the availability and application of automatic AF functions to allow an optimal balance between achieving an adequate dialysis dose and curtailing treatment costs. Therefore, they suggested that an appropriate AutoFlow factor should be carefully and empirically adapted to the individual needs of the patient by increasing this factor stepwise until the prescribed target dose has been reached (9).

Our study is the first to predict an appropriate AF factor with a mathematical model which was validated by examining the effects of three different Qd's on delivered dose of dialysis. Mathematical modelling suggested that AF depended on the characteristics of the membrane and the extracorporeal blood circuit especially the ratio (KoA/Qbw), and showed that dialytic clearance is performed at an AF factor

TABLE 5. *Dialysate saving potential via the application of the AutoFlow function*

	Dialysate flow rate (Qd)		
	Qd with AF	Qd 500	Average savings
Average dialysate flow rate (mL/min)	404	500	–19.2%
Cumulated dialysate volume over a session (L)	96	120	–20%
Purified water over a session (L)	89	112	–20%
Acid concentrate (L)	2.74	3.42	–20%
Life of bicarbonate powder (min)	445	360	+23%
No. of Sessions performed by a tank of 1000 L of acid concentrate	365	292	+25%

Note: Dilution parameter (1 + 34): 1; Acid concentrate—1225; Bicarbonate—32 775; Purified water.

between 1.2 to 1.5 with values of KoA in the range of two to five times that of the Qb. The minimum value of the AF factor that ensured the maximum saving in dialysis fluid consumption is equal to 1 and observed with high mass transfer area coefficient. The maximum value tended toward 2 and was observed at higher blood flow rates associated with a low KoA. This model suggests that the value of increasing dialysate flow to compensate for a low vascular access flow (when blood is not flowing) is likely to be small.

In vivo, because dialysis time (t), ultrafiltration volume (convective K), recirculation, blood flow, dialyzers, anticoagulation and urea distribution volume (V) of the patients were constant during the study period, we confirmed that increasing Qd more than the model predicts had a small effect in the Kt/V (less than 2% when the AF factor exceeds 2). In our study, the number of patients reaching a target Kt/Vw.ocm of 1.2 or greater did not change after increasing Qd more than predicted by the model. We noted that several studies have showed a better agreement between the single pool Kt/Vw.ocm (because of overestimation of urea distribution volume by the Watson formula) and the eKt/V (18).

In contrast to this study, some authors have found that increasing Qd from 500 to 800 mL/min resulted in a greater gain of urea clearance than predicted by classic urea kinetic modeling formulas (19,20). It should be cautioned, however that this was observed in vitro especially and when the KoA of the dialyzer was inconstant (10). Leypoldt and colleagues suggested that the increase in KoA in vitro associated with increasing dialysate flow rate could result from a reduced dialysate boundary layer thickness or improved flow distribution in the dialysate compartment (20). Soon thereafter, dialyzers became available with spacer yarns in the fiber bundle or fibers with undulations to improve dialysate flow distribution. Recently, Bhimani et al. showed that KoA for urea and phosphate was statistically independent of dialysate flow rate during clinical use of dialyzers containing fibers with undulations (8). Currently, improvements in dialyzer design have reduced the importance of mass transfer resistances from blood and dialysate stagnant fluid layers such that urea mass transfer-area coefficients are largely determined by the surface area and the intrinsic permeability of the dialysis membrane. Thus, urea mass transfer-area coefficients of modern hollow fiber dialyzers are considered to be constants. Hootkin has showed the effect of increasing dialysate flow rate on urea clearance, assuming a constant value of urea KoA from 500 to either 800 or 1000 mL/min, results in a small increase in urea clearance (16). Küz et al. found, with fiber bundle design leading to an opitimized dialysate flow distribution, only a small decrease in clearance value when reducing the dialysate flow rate from 500 mL/mn to 400 mL/mn (21). We recall that our model has been validated in vivo using high flux membrane with fiber undulations. Therefore, our model may underestimate the AF factor with old dialyzers that not ensure a constant KoA. However the magnitude changes of KoA in these membranes in vivo (less than 5–7%) (22,23) would not significantly alter predictions of our model because the blood side resistance plays a greater role in determining KoA when fibers are perfused with blood (8). In this case, the use of a simplified equation, which takes into consideration Qb not Qbw and thus slightly overestimates the real AF could offset the increase in KoA with Qd.

Although the model takes into account ultrafiltration and convective clearance of small solutes (Eq. 1), it should be emphasized that the present study only validates this mathematical modelling in standard hemodialysis and these results cannot be translated directly to hemodiafiltration without direct confirmation.

Water is an expensive commodity, and with predictions showing an expected increase in its costs in the future, this is a crucial issue that needs to be addressed during the delivery of modern dialytic therapies. Our results showed that the AutoFlow function has the potential to save osmosis water, the concentration of acid and of bicarbonate, and the energy that is normally required to heat the dialysate, without compromising the dose of dialysis. This finding was postulated also by Kult and Stapf (9). Saving the bicarbonate powder can perform the dialysis session without incident of conductivity and on-line production, especially when it is extended.

CONCLUSION

In many parts of the world water is a precious and expensive commodity. For this reason, techniques that allow dialysate consumption to be reduced without compromising the delivery of therapy are important. The model described in this paper seems to be useful in predicting an appropriate AutoFlow factor that achieves an optimal urea clearance with a significant saving in dialysis fluid consumption. Increasing the dialysate flow rate more than the model predicts had only a modest impact on the Kt/V.

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