

# Dialysate Flow Rate and Delivered $Kt/V_{\text{urea}}$ for Dialyzers with Enhanced Dialysate Flow Distribution

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## Summary

**Background and objectives** Previous *in vitro* and clinical studies showed that the urea mass transfer-area coefficient ( $K_oA$ ) increased with increasing dialysate flow rate. This observation led to increased dialysate flow rates in an attempt to maximize the delivered dose of dialysis ( $Kt/V_{\text{urea}}$ ). Recently, we showed that urea  $K_oA$  was independent of dialysate flow rate in the range 500 to 800 ml/min for dialyzers incorporating features to enhance dialysate flow distribution, suggesting that increasing the dialysate flow rate with such dialyzers would not significantly increase delivered  $Kt/V_{\text{urea}}$ .

**Design, setting, participants, & measurements** We performed a multi-center randomized clinical trial to compare delivered  $Kt/V_{\text{urea}}$  at dialysate flow rates of 600 and 800 ml/min in 42 patients. All other aspects of the dialysis prescription, including treatment time, blood flow rate, and dialyzer, were kept constant for a given patient. Delivered single-pool and equilibrated  $Kt/V_{\text{urea}}$  were calculated from pre- and postdialysis plasma urea concentrations, and ionic  $Kt/V$  was determined from serial measurements of ionic dialysance made throughout each treatment.

**Results** Delivered  $Kt/V_{\text{urea}}$  differed between centers; however, the difference in  $Kt/V_{\text{urea}}$  between dialysate flow rates of 800 and 600 ml/min was NS by any measure (95% confidence intervals of  $-0.064$  to  $0.024$  for single-pool  $Kt/V_{\text{urea}}$ ,  $-0.051$  to  $0.023$  for equilibrated  $Kt/V_{\text{urea}}$ , and  $-0.029$  to  $0.099$  for ionic  $Kt/V$ ).

**Conclusions** These data suggest that increasing the dialysate flow rate beyond 600 ml/min for these dialyzers offers no benefit in terms of delivered  $Kt/V_{\text{urea}}$ .

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## Introduction

The dose of hemodialysis delivered in a single treatment is commonly expressed in terms of  $Kt/V_{\text{urea}}$ , where  $K$  is the clearance of urea,  $t$  is the treatment time, and  $V$  is the urea distribution volume. Michaels (1) showed that clearance ( $K$ ) is related to blood flow rate ( $Q_B$ ), dialysate flow rate ( $Q_D$ ), and the product of the mass transfer coefficient and membrane surface area ( $K_oA$ ) by the following equation.

$$K = Q_B \left[ \frac{\exp\left(\frac{K_oA(1 - Q_B/Q_D)}{Q_B}\right) - 1}{\exp\left(\frac{K_oA(1 - Q_B/Q_D)}{Q_B}\right) - \frac{Q_B}{Q_D}} \right]$$

Michaels treated  $K_oA$  as a constant for a given dialyzer-solute combination. However, Leyboldt *et al.* (2) showed that increasing the dialysate flow rate from the traditional 500 ml/min to 800 ml/min increased  $K_oA$  for urea by 14% in an *in vitro* study using a variety of dialyzers. They suggested that this increase in  $K_oA$  could result from improved flow distribution through the dialysate compartment or a decrease in boundary layer resistance to mass transfer on the dialysate side of the membrane. Subsequently, we

showed that  $K_oA$  for urea also depends on dialysate flow rate during clinical dialysis (3), and Hauk *et al.* (4) found a greater than predicted increase in  $Kt/V_{\text{urea}}$  when dialysate flow rate was increased from 500 to 800 ml/min. These observations led to the widespread use of higher dialysate flow rates for routine clinical dialysis.

Recognizing that poor dialysate flow distribution might negatively affect dialyzer performance, dialyzer manufacturers introduced features, such as hollow fiber undulations, spacer yarns, and changes in fiber packing density to improve flow distribution through the dialysate compartment (5). These improvements in dialysate flow distribution were accompanied by an increase in urea clearance (5), and subsequently, we showed that increasing the dialysate flow rate no longer led to an increase in  $K_oA$  when the dialyzers contained hollow fibers with undulations (6).

If  $K_oA$  is constant, the Michaels equation predicts only a modest change in urea clearance as dialysate flow rate changes over the range 500 to 800 ml/min. For example, increasing the dialysate flow rate from 600 to 800 ml/min would result in only a 4% increase

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in urea clearance for a blood flow rate of 400 ml/min and a hematocrit of 35%. On the basis of the predicted modest increase in urea clearance, we hypothesized that increasing the dialysate flow rate from 600 to 800 ml/min in dialyzers incorporating features to enhance dialysate flow distribution would not produce a clinically significant increase in delivered  $Kt/V_{\text{urea}}$ .

## Materials and Methods

### Study Population

Subjects were enrolled from patients receiving chronic hemodialysis at the University of Louisville (center 1), Vanderbilt University (center 2), and the University of California Davis (center 3). To participate in the study, subjects were required to be  $\geq 18$  years of age, to have been undergoing chronic hemodialysis three times a week with a stable treatment prescription, to have not been hospitalized for a significant illness related to their kidney failure except for vascular access surgery for at least 3 months, and to have an arteriovenous fistula or graft capable of routinely delivering a blood flow rate of 400 ml/min. Exclusion criteria included noncompliance with the dialysis prescription, a current malignancy involving sites other than skin, a history of drug or alcohol abuse within the previous 6 months, pregnancy, a positive test for hepatitis B surface antigen within the previous 30 days, and a known HIV infection.

### Study Design

The objective of the study was to test the hypothesis that increasing the dialysate flow rate from 600 to 800 ml/min would not significantly increase the delivered  $Kt/V_{\text{urea}}$ . The study used a multi-center prospective randomized cross-over design in which subjects were randomly assigned to be dialyzed according to an ABAB or BABA schedule, where A represents three consecutive dialysis treatments with a dialysate flow rate of 600 ml/min, and B represents three consecutive treatments with a dialysate flow rate of 800 ml/min. Randomization was performed using sealed envelopes containing either an ABAB or BABA schedule and was blocked by center. The primary outcome was the delivered single-pool  $Kt/V_{\text{urea}}$  (spKt/V), which was measured during the final treatment session of each group of three treatments. Secondary outcomes were equilibrated  $Kt/V_{\text{urea}}$  (eKt/V) and  $Kt/V$  determined from measurements of ionic dialysance ( $Kt/V_{\text{ID}}$ ). The study was reviewed by the institutional review board at each center and was registered with ClinicalTrials.gov (identifier NCT00962000).

### Dialysis Treatments

Each subject followed their usual dialysis prescription throughout the study, apart from the dialysate flow rate, which was set at 600 or 800 ml/min depending on the preset ABAB or BABA sequence. Ultrafiltration volumes were set according to clinical need. Treatments were performed with single-use Polyflux Revaclear or Revaclear MAX dialyzers (selected on the basis of previous dialyzer prescription) and Phoenix dialysis machines (Gambro Renal Products, Lakewood, CO) at center 1 and 2008K dialysis machines (Fresenius, Medical Care, Lexington, MA) at

centers 2 and 3. The Revaclear dialyzers incorporate both fiber undulations and an increased packing density to enhance flow distribution through the dialysate compartment.

### Measurement of Kt/V

spKt/V and eKt/V were calculated using pre- and post-dialysis blood urea nitrogen (BUN) concentrations according to Daugirdas (7) and Daugirdas and Schneditz (8). The predialysis BUN sample was drawn from the arterial access needle before dialysis was started and before the needle was flushed with saline or heparin. At the completion of dialysis, the ultrafiltration rate was minimized, and dialysate flow through the dialyzer was stopped. The blood flow rate was decreased to 100 ml/min, and the postdialysis BUN sample was drawn from the sample port in the arterial blood line after 15 seconds. BUN concentrations were measured by standard clinical laboratory methods.

For two centers,  $Kt/V_{\text{ID}}$  was determined for each study treatment using the Diascan and on-line clearance features of the Phoenix and 2008K dialysis machines, respectively, and a volume of urea distribution was calculated from anthropometric data (9). The third center did not have the capability to measure ionic dialysance.

### Sample Size

The sample size was calculated on the basis of a within-subject between-treatments SD of 0.21 for spKt/V. Using this value, which was obtained from an analysis of data from 50,000 patients, the sample size needed to detect a difference of 0.1 in spKt/V between the two dialysate flow rates with 90% power was 38 patients. To allow for equal distribution of patients between the three centers and some contingency for possible drop-outs, a final sample size of 42 was chosen.

### Statistical Analyses

Differences between  $Kt/V$  at the two different dialysate flow rates were assessed by ANOVA. The three centers and the two flow rates were treated as fixed effects, and the subjects within centers were modeled as a random effect. These analyses were performed using SAS statistical software (Cary, NC).

## Results

### Subjects

Forty-two subjects (16 women and 26 men) were enrolled in the study. Their average age was 50 years (range, 19 to 85 years). They had been receiving hemodialysis for an average of 81 months (range, 7 to 264 months) at the time of the study. Their average predialysis weight was 84 kg (range, 48 to 147 kg). The cause of their kidney failure included hypertension (14 subjects), diabetes (11 subjects), glomerulonephritis (9 subjects), systemic lupus erythematosus (2 subjects), polycystic kidney disease (2 subjects), reflux nephropathy (1 subject), gout (1 subject), Alport syndrome (1 subject), and acute kidney injury (1 subject). Blood access was obtained via an arteriovenous fistula in 26 subjects and via a polytetrafluoroethylene graft in 16 subjects.

**Dialysis Treatments**

Data from 16 of the 168 treatments were excluded from the data analysis. One treatment was performed at an incorrect blood flow rate, the prescribed treatment time was not used for 10 treatments, and the pre- or postdialysis BUN was not obtained for five treatments. All subjects completed at least one treatment with each of the two dialysate flow rates.

Details of the dialysis treatments included in the analysis of  $spKt/V$  and  $eKt/V$  are presented in Table 1. Measurements of  $Kt/V$  were made at a median blood flow rate of 450 ml/min (interquartile range [IQR], 400 to 450 ml/min). Blood flow rates differed significantly between centers ( $P = 0.011$ ), with centers 1 and 3 having higher blood flow rates than center 2. However, blood flow rates did not differ between dialysate flow rates ( $P = 0.28$ ). The median treatment time was 210 minutes (IQR, 184 to 240 minutes). Treatment times were shorter at center 3 than at the other two centers ( $P = 0.001$ ) but did not differ between dialysate flow rates ( $P = 0.67$ ). Ultrafiltration rates were set according to the clinical needs of the patient. The median overall fluid removal was 2.80 L (IQR, 1.8 to 3.5 L). There were no differences in fluid removal between centers ( $P = 0.32$ ) or between the two dialysate flow rates ( $P = 0.32$ ). Anticoagulation was obtained using heparin given as a loading dose (mean, 2612 IU; range, 0 to 8000 IU) and constant infusion (mean, 971 IU/h; range, 0 to 3000 IU/h). Heparin doses remained constant for each individual patient for the duration of the study.

Ionic dialysance and  $Kt/V_{ID}$  were determined for every treatment at two of the three centers. The data from 52 of the 336 treatments were excluded from the analysis of ionic dialysance and  $Kt/V_{ID}$  because of deviations from the prescribed treatment time or blood flow rate. As with the blood-based determinations, blood flow rates were significantly different between the two centers ( $P = 0.012$ ) but not between the two dialysate flow rates ( $P = 0.29$ ). There were no differences in treatment time or fluid removal between the two centers or the two dialysate flow rates.

**Delivered  $Kt/V$**

Adjusted means and standard errors for  $Kt/V$  at dialysate flow rates of 600 and 800 ml/min are presented in Table 2. Delivered  $Kt/V$  differed significantly between centers ( $P = 0.018$  and  $0.006$  for  $spKt/V$  and  $eKt/V$ , respectively), being highest at center 2 and lowest at center 1. However, there was no difference in either  $spKt/V$  or  $eKt/V$  between dialysate flow rates regardless of the order of the treatments (ABAB or BABA). The difference in  $spKt/V$  between dialysate flow rates of 800 and 600 ml/min was  $-0.024$ , with a 95% confidence interval of  $-0.064$  to  $0.024$ , and the difference in  $eKt/V$  between dialysate flow rates of 800 and 600 ml/min was  $-0.014$ , with a 95% confidence interval of  $-0.051$  to  $0.023$ .

Ionic dialysance and  $Kt/V_{ID}$  were determined for all study treatments at centers 1 and 2 (Table 3). Ionic dialysance differed significantly between the two centers and between the two dialysate flow rates. The mean difference in ionic dialysance between dialysate flow rates of 800 and 600 ml/min was 6.89 ml/min, with a 95% confidence interval of 3.98 to 9.81 ml/min. In spite of this difference,

**Table 1. Treatment parameters for blood-based determination of delivered  $Kt/V$**

	Dialysate flow rate							
	Center 1		Center 2		Center 3		All Centers	
	600 ml/min	800 ml/min	600 ml/min	800 ml/min	600 ml/min	800 ml/min	600 ml/min	800 ml/min
Treatment time (min)	210 (210 to 245)	210 (210 to 240)	224 (180 to 245)	227 (209 to 241)	184 (180 to 214)	190 (180 to 210)	210 (182 to 240)	210 (190 to 240)
Blood flow rate (ml/min)	450 (450 to 450)	450 (450 to 450)	400 (400 to 450)	400 (400 to 450)	450 (400 to 450)	450 (400 to 450)	450 (400 to 450)	450 (400 to 450)
Ultrafiltration volume (L)	3.0 (1.8 to 3.6)	2.8 (2.2 to 5.1)	3.3 (1.7 to 4.3)	2.8 (1.9 to 3.5)	2.8 (1.4 to 3.4)	2.5 (1.9 to 3.0)	2.8 (1.7 to 3.7)	2.6 (1.9 to 3.4)

The data are presented as the medians and interquartile ranges. Blood flow rates ( $P = 0.011$ ) and treatment times ( $P = 0.001$ ), but not ultrafiltration volume, differed between centers. Blood flow rates, treatment time, and ultrafiltration volume did not differ between dialysate flow rates.

**Table 2. Delivered dose of dialysis at dialysate flow rates of 600 ml/min and 800 ml/min**

	Dialysate flow rate							
	Center 1		Center 2		Center 3		All Centers	
	600 ml/min	800 ml/min	600 ml/min	800 ml/min	600 ml/min	800 ml/min	600 ml/min	800 ml/min
spKt/V	1.55 ± 0.19	1.57 ± 0.21	1.82 ± 0.23	1.72 ± 0.22	1.62 ± 0.25	1.62 ± 0.21	1.66 ± 0.25	1.63 ± 0.21
eKt/V	1.29 ± 0.16	1.31 ± 0.17	1.52 ± 0.17	1.44 ± 0.17	1.32 ± 0.20	1.32 ± 0.18	1.37 ± 0.20	1.35 ± 0.18

The data are presented as the means ± SD. spKt/V and eKt/V differed significantly between centers ( $P = 0.018$  and  $P = 0.006$  for spKt/V and eKt/V, respectively). For the three centers combined, the difference in spKt/V and eKt/V between the two dialysate flow rates was not significant ( $-0.024$  with 95% confidence limits of  $-0.064$  and  $0.024$  for spKt/V and  $-0.014$  with 95% confidence limits of  $-0.051$  and  $0.023$  for eKt/V). spKt/V, single-pool Kt/V<sub>urea</sub>; eKtV, equilibrated Kt/V<sub>urea</sub>.

**Table 3. Ionic dialysance and Kt/V<sub>ID</sub> at dialysate flow rates of 600 and 800 ml/min**

	Dialysate flow rate					
	Center 1		Center 2		All Centers	
	600 ml/min	800 ml/min	600 ml/min	800 ml/min	600 ml/min	800 ml/min
Ionic dialysance (ml/min)	256 ± 18	262 ± 19	243 ± 14	251 ± 17	250 ± 17	257 ± 19
Kt/V <sub>ID</sub>	1.33 ± 0.19	1.32 ± 0.18	1.59 ± 0.22	1.68 ± 0.39	1.46 ± 0.24	1.49 ± 0.35

The data are presented as the means ± SD. Ionic dialysance and Kt/V<sub>ID</sub> differed significantly between centers (both  $P < 0.001$ ). For the two centers combined, the difference in ionic dialysance between the two dialysate flow rates was significant (6.89 with 95% confidence limits of 3.98 and 9.81), whereas the difference for Kt/V<sub>ID</sub> was not significant (0.035 with 95% confidence limits of  $-0.029$  and  $0.099$ ). Kt/V<sub>ID</sub>, ionic dialysance.

the difference in Kt/V<sub>ID</sub> between dialysate flow rates of 800 and 600 ml/min was NS at 0.035, with a 95% confidence interval of  $-0.029$  to  $0.099$ .

## Discussion

Adequate solute removal by hemodialysis is frequently defined in terms of Kt/V<sub>urea</sub>. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines recommended a target spKt/V of 1.4 for patients treated on a thrice weekly schedule and a minimally adequate delivered spKt/V of 1.2 (10). Subsequently, that minimally adequate dose was adopted by the Centers for Medicare and Medicaid Services as a clinical performance measure for out-patient dialysis facilities in the United States. Because little can be done to change the volume of distribution (V) of a given patient and because facilities and many patients constrain the length of a dialysis treatment (t), the focus has been on maximizing urea clearance (K) to ensure delivery of a spKt/V of 1.2 or greater.

Clearance is a function of the blood and dialysate flow rates and the K<sub>o</sub>A of the dialyzer (1). The blood flow rate is a function of the quality of the patient's blood access and limitations imposed by extracorporeal circuit, including the needle size and the elastic recoil of the pump segment of the blood tubing set (11,12). These considerations limit routine blood flow rates to 500 ml/min, or less, for most patients. K<sub>o</sub>A is considered a fundamental property of a dialyzer, independent of the blood and dialysate flow

rates, with clearance increasing as K<sub>o</sub>A increased. However, studies in the 1990s suggested that K<sub>o</sub>A, and hence clearance, could be increased significantly by increasing the dialysate flow rate (2–4). These observations led to the widespread use of dialysate flow rates of 700 to 800 ml/min to maximize clearance and Kt/V<sub>urea</sub>.

Recognizing that poor distribution of flow through the dialysate compartment might compromise solute mass transfer, dialyzer manufacturers implemented a number of changes in dialyzers designed to improve flow distribution and enhance solute mass transfer. These changes included spacer yarns in the fiber bundle, fiber undulations, changes in fiber packing density, and improvements in the flow distributors at the entrance and exit of the dialysate compartment (2,5,13). We showed that there was little improvement in K<sub>o</sub>A when the dialysate flow rate was increased from 500 to 800 ml/min under routine clinical conditions when dialyzers incorporated these features (6). One implication of that finding was that the use of high dialysate flow rates would no longer confer an advantage in terms of delivered Kt/V<sub>urea</sub>. The results of this study, which used dialyzers with fiber undulations and an increased fiber packing density, support that hypothesis by showing no difference in delivered urea Kt/V between dialysate flow rates of 600 and 800 ml/min.

Delivered Kt/V<sub>urea</sub> was determined using both blood-based and dialysate-based methods. When Kt/V<sub>urea</sub> is calculated from pre- and postdialysis urea concentrations, the



clearance term represents a whole-body clearance, which may be influenced by patient factors independent of the dialyzer performance. In contrast, ionic dialysance is an instantaneous measure of dialyzer performance independent of other factors. We found a small, but significant, increase of almost 7 ml/min in ionic dialysance when the dialysate flow rate was increased from 600 to 800 ml/min. A 7 ml/min difference in ionic dialysance is equivalent to an additional 1.5 L of total clearance assuming our average treatment time of 214 minutes or a 3.8% increase in  $Kt/V_{\text{urea}}$  assuming a urea distribution volume of 40 L. The observed increase in  $Kt/V_{\text{ID}}$  was 2.1%. Thus, the ionic dialysance data also support the hypothesis that increasing the dialysate flow rate from 600 to 800 ml/min has no clinically meaningful effect on delivered  $Kt/V_{\text{urea}}$  for dialyzers incorporating features that enhance dialysate distribution.

The observed increase in ionic dialysance of 7 ml/min compares with an increase of 12 ml/min predicted using the Michaels equation (1) for a blood flow rate of 433 ml/min and a hematocrit of 35%. The clearance predicted by the Michaels equation is a purely diffusive clearance, whereas the clearance measured during dialysis is a combination of diffusion and convection, including internal filtration and back-filtration in the dialyzer, the magnitude of which might depend on the dialysate flow rate. Thus, the ability of the Michaels equation to predict changes in clearance during clinical dialysis and changes in  $Kt/V_{\text{urea}}$  on the basis of those predicted changes in clearance is limited, particularly when the changes in diffusive clearance are small.

Our findings are likely to be generally applicable. We show that there is no difference in delivered  $Kt/V_{\text{urea}}$  when the dialysate flow rate is increased from 600 to 800 ml/min by both blood- and dialysate-based methods. The same result was obtained in three dialysis centers using two different types of dialysis machine, commonly used dialysis prescriptions (blood flow rates of 400 to 500 ml/min and treatment times of 3 to 4 hours), and dialyzers of two different surface areas (1.4 and 1.8 m<sup>2</sup>). One possible limitation is that our results were obtained with a single type of dialyzer. We previously reported that  $K_{\text{oA}}$  for urea was independent of dialysate flow rate, not only for the type of dialyzer used in this study but also for another commonly used type of dialyzer (6). Taken together with the results of this study, these data suggest that our findings could apply to other contemporary dialyzers designed with features that enhance dialysate flow distribution. However, confirmation of that possibility will require additional study. Our findings also have practical application. Reducing the dialysate flow rate from 800 to 600 ml/min reduces consumption of water and dialysate concentrate by 25% and lessens the wear and tear on water treatment and other fluid-handling systems, allowing resources to be reallocated to other aspects of the dialysis treatment that might more positively benefit patients. For concentrate, alone, a 25% reduction in use could correspond to a savings of about \$1.50 for a 4-hour treatment depending on the facility's cost for concentrate. Importantly, a reduction in dialysate flow rate from 800 to 600 ml/min is unlikely to compromise the removal of larger solutes because  $K_{\text{oA}}$  and diffusive clearance of those sol-

utes are dependent on membrane permeability and essentially independent of dialysate flow rate in the range used in this study (6).

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#### Disclosures

None.

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