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Accuracy of urea removal estimated by kinetic models

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Accuracy of urea removal estimated by kinetic models. The most accurate method for assessing the dialysis dose delivered during high efficiency/flux hemodialysis has not been established. Most current indices of dialysis dose are based on blood-side urea measurements, and thus estimate urea removal. Unfortunately, these methods may lead to inappropriately short dialysis during high flux or high efficiency dialysis, perhaps because of inaccuracies in estimating the amount of urea removal. It is unknown whether these clearance-based approaches can accurately predict either absolute or fractional net urea removal, the latter being equivalent to the solute removal index (SRI). Therefore, we compared the urea removal calculated by five blood-side kinetic methods: (1) urea reduction ration, (2) 1-pool, (3) 2-pool models, and the (4) Smye and (5) Daugirdas formulae. These were compared with the gold standard measurement by direct dialysate quantification. Eight stable patients receiving high-flux hemodialysis were studied over four sessions each. BUN was measured at 0, 45 minutes, 90 minutes, end dialysis, one hour after dialysis (equilibrium value), and 48 hours later. Total body water was determined from the dialysate urea removal; the urea generation rate was calculated using one hour post-dialysis and 48-hour BUN values. Both the total body water and urea generation rate were provided to the 1- and 2-pool models to optimize accuracy. The urea reduction ratio overestimated SRI. The 1-pool model overestimated both absolute urea removal and SRI in 28 of 32 sessions. The 2-pool model slightly underestimated both absolute urea removal and SRI. In contrast, the Smye and Daugirdas formulas accurately estimated SRI. We conclude that: (1) The 1-pool model consistently overestimates urea removal, which leads to inappropriately short dialysis times. (2) The 2-pool model, provided with an accurate TBW, slightly underestimates urea removal. (3) The Smye and Daugirdas methods accurately predict SRI and are sufficiently accurate to quantify dialysis dose and adequacy. Because the Smye and Daugirdas methods are operationally and mathematically simpler than 1- or 2-pool kinetic modeling, we propose that they be tested in a randomized controlled trial of dialysis adequacy during high efficiency or high flux hemodialysis.

Dialysis adequacy has important implications for long-term outcome on dialysis. Accurate estimation of prescribed and delivered dialysis dose is a central issue in modern dialysis therapy. Although urea is not the uremic toxin, all current indices of dialysis dose are based on urea measurements, and thus set urea removal as the major goal of hemodialysis [1–4]. The most common method for measuring dialysis dose employs a blood-side mathematical model based on the premise that urea follows single pool kinetics during and after dialysis (Kt/V), and thus proposes that dialysis dose can be measured using BUN measurements before and immediately after dialysis. This model was clinically validated for conventional dialysis using cellulose acetate dialysis based on data from the National Cooperative Dialysis Study [5].

However, since the early 1980's, there have been major improvements in dialysis technology, including use of higher blood and dialysate flow rates, and new high flux and high efficiency dialyzer membranes. With the advent of faster dialysis, the blood urea concentration departs significantly from single pool kinetics [2, 6–9]. At the end of dialysis, BUN rebounds rapidly over 30 to 60 minutes until a new equilibrium state is reached. The end dialysis BUN does not accurately reflect the urea content of the body because a substantial urea disequilibrium between blood and cell compartments exists during dialysis, which relaxes after dialysis. Thus, urea kinetics are more complicated during fast dialysis, raising questions about the applicability of current models during high efficiency or high flux hemodialysis. In particular, use of single pool models for prescribing dialysis may result in overestimation of delivered dialysis which could lead to inadequate prescribed and delivered dialysis.

The most accurate method for assessing the delivered dialysis dose during high efficiency/flux hemodialysis has not been established. More complicated blood-side models have been proposed which include either multiple compartments or blood pools [1, 2, 8–11]. These models more accurately predict BUN during and after dialysis; however, they require the estimation of additional parameters such as compartment volumes, and the urea mass transfer coefficient (K_c) or regional pool blood flows. Some of the new parameters, especially the K_c and blood flows, might vary from session to session, introducing additional complexity. These models are thought to be too complicated for routine clinical use.

Several simpler formulas have been developed recently to circumvent some of these problems. Smye has proposed a new method whereby the equilibrium BUN is predicted by three blood samples taken during dialysis: the routine pre- and post-dialysis BUN along with an intradialytic sample taken at 70 minutes [12]. Daugirdas has proposed an even simpler method where a single pool estimate of Kt/V is modified according the speed of dialysis (K/V) to obtain a double pool estimate of Kt/V. The urea reduction ratio, attractive because of its simplicity, has also been proposed as a measure of dialysis dose [13, 14]. All of these formulas can be transformed by mass balance considerations to calculate absolute or fractional urea removal. However, the accuracy of these techniques have not been validated in high-efficiency high flux dialysis patient populations.

Recently, dialysate-side methods have been proposed which directly measure actual urea removal [2–4, 15, 16]. The results can be expressed either as the *absolute* amount of urea removed (grams per session), or the *fractional* urea removal (expressed as

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a percentage of predialysis body urea content). These methods are thought to be most accurate, since they circumvent errors caused by compartment/blood pool effects. Indeed, we have recently proposed that solute reduction index (SRI), a measure of *fractional* net urea removal during dialysis, be considered as a simpler and more accurate measurement of dialysis dose [4]. SRI is the net urea removal (total urea removed minus urea generated during dialysis) divided by the predialysis body urea content. These methods require that the dialysate urea concentration and flow rate be directly measured using special equipment or modifications to the dialysis machines [4]. However, this introduces additional complexity, and may be to difficult for routine clinical usage. An easier alternative to quantify dialysis dose would be to estimate urea removal from blood samples taken during dialysis.

The purpose of this study was to determine which model(s) provide the most accurate estimate of either absolute urea removal or SRI during dialysis. Therefore, we determined whether five kinetic models/formulas based only on blood-side measurements collected *during* dialysis can accurately predict absolute urea removal or SRI: (1) urea reduction ratio, (2) 1-pool model, (3) simplified 2-pool model, (4) Smye formula, and (5) Daugirdas equation. We measured absolute urea removal and SRI by the gold standard of direct dialysate quantification.

Methods

Blood and dialysate sampling

Eight stable patients receiving high-flux hemodialysis were studied over four sessions each. Dialysis time was constant for each patient; blood flow rates were constant during each session. Blood pumps were calibrated immediately before each hemodialysis session at a negative pressure of 100 mm Hg with room temperature saline. Dialysis urea removal was measured by collecting the spent dialysate into large tanks. Bacterial contamination was minimized by bleaching the tanks between use, and collecting the total dialysate in three to four collections of 60 to 90 minutes each. At the end of each collection, the tank was stirred, weighed, and a 15 cc aliquot was removed, filtered with a 0.45 μm filter, and frozen. BUN was measured at 0, 45, 90 minutes, end dialysis, one hour post-dialysis (equilibrium value), and 48 hours (C_0, C_{45}, C_{90}, C_{Td}, $C_{1\ hr}$). The samples during and at the immediate end of dialysis were measured with the blood pump running. Venous port samples were obtained at 45 and 90 minutes to allow calculation of dialyzer urea clearance. Recirculation was determined by occluding the access, without changing the blood flow rate. To increase accuracy, several of the blood samples (C_0, C_{45}, C_{Td}) were obtained in duplicate. All dialysate and BUN samples were analyzed in triplicate using an autoanalyzer (Baxter Paramax 720ZX). In preliminary studies, we showed that the Baxter autoanalyzer could accurately measure urea in aqueous solutions.

Calculations

Appendix A contains the equations. Dialyzer urea clearance and recirculation were obtained at 45 and 90 minutes (equations 1 and 2); the values differed by $< 1\%$. Total body water (TBW or V) was determined by dividing DDQ by the change in BUN from predialysis to one hour post-dialysis (equilibrium value), adjusted for urea generation (equation 3). The urea generation rate (UGR) was calculated using the one hour post-dialysis and 48 hour BUN values (equation 4). Both TBW and UGR were provided to the 1- and 2-pool models to optimize accuracy. SRI was calculated by a standard formula (equation 5) [4]. Equilibrium Kt/V was calculated from the predialysis and equilibrium BUN (corrected for urea generation during the rebound phase) using equation 6.

Urea reduction ratio

The urea reduction ratio has been recommended as a means of quantifying delivered dialysis dose [13, 14]. The urea reduction ratio was calculated (equation 7) and assumed to represent the fractional urea removed during dialysis (SRI).

One pool model

A variable volume one pool model (**Appendix B**) was provided with C_0, K, V, and UGR. The model was run for Td minutes, and the net urea removal (urea removed − urea generated) and SRI were calculated by mass balance (equation 8). This model differs from the usual KT/V model since V was supplied to the model, and not inferred from the data.

Two pool model

A variable volume two pool model (**Appendix B**) was provided with C_0, C_{45}, C_{90}, Td, K, V, UGR. The water mass transfer coefficient was set to 3.8 liter^2/min [17]. The ratio of ECF/TBW was set to 0.25, as we have determined previously [9]. Sensitivity analysis showed that changes in this ratio does not alter SRI or urea removal. The model was run to find the best urea mass transfer coefficient (K_c). The net urea removal and SRI were calculated by mass balance (equation 9).

Smye method

The Smye formula calculates an equilibrium BUN (formula 21 in [12]). SRI was calculated directly after correcting the equilibrium BUN for urea generation during the one hour period post-dialysis (equation 10). We assumed that the pre- and post-dialysis volume was equal to 0.58 times body wt, as assumed in the Smye formula.

Daugirdas method

Daugirdas has proposed that a double pool Kt/V can be estimated from a formula based only on single pool Kt/V, and the rate of dialysis (K/V). Therefore, we calculated the single pool Kt/V using a 'second-generation' formula [18] (equation 6), and used it to calculate the double pool Kt/V (equation 11) [19]. This formulation does not require an accurate V, since the K/V term can be calculated from single pool Kt/V by dividing by t. The double pool Kt/V was then converted to SRI by an exponential transformation (equation 12).

Statistics

We used paired and unpaired Student's *t*-tests as appropriate. Correlations were calculated using the Pearson product moment method. A P value less than 0.05 was taken as indicative of statistical significance. Data expressed as mean ± 1 SD.

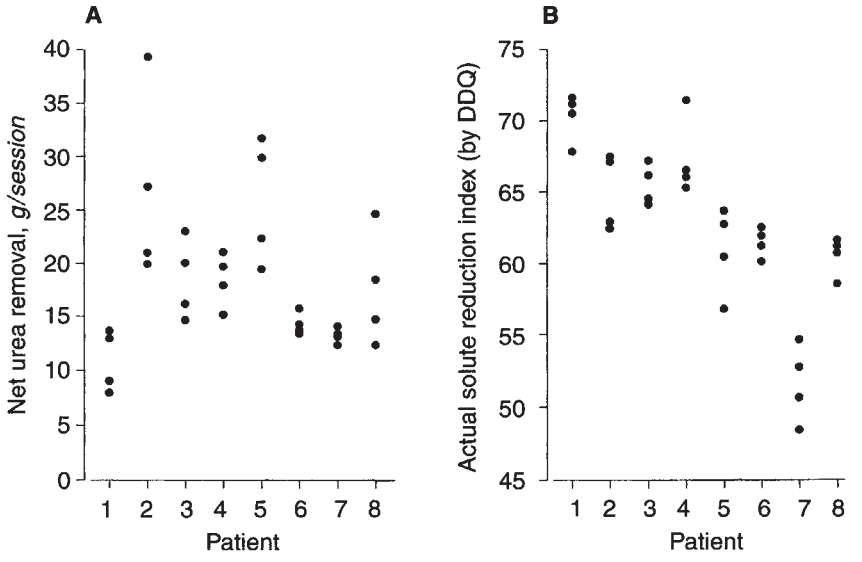

Fig. 1. *Absolute urea removal and solute reduction index measured in individual hemodialysis sessions.* Each dot represents data obtained from a single dialysis session. Data from each patient is displayed in a unique column, labeled 1 to 8. **(A)** Absolute urea removal measured by direct dialysate quantification; **(B)** SRI calculated from equation 5.

Table 1. SRI and equilibrium Kt/V for individual patients over four dialysis sessions

	SRI		Equilibrium Kt/V_{eq}	
Patient	Mean	COV	Mean	COV
1	70.45	2.51	1.39	6.03
2	64.97	4.12	1.19	8.85
3	65.48	2.17	1.18	2.78
4	67.35	4.10	1.21	7.92
5	60.89	5.06	1.07	10.04
6	61.43	1.67	1.00	2.69
7	51.59	5.14	0.78	3.97
8	60.63	2.42	0.99	4.34
Mean	62.84	3.40	1.10	5.83
SD	5.69	1.37	0.18	2.83

SRI is measured from dialysate urea collection using equation 5. Equilibrium Kt/V is calculated from pre-dialysis BUN and equilibrium BUN (corrected for urea generation) using equation 6. COV is coefficient of variation.

Results

Patient demographics

Eight stable ESRD patients were studied: five men and three women. The diagnoses included five patients with ESRD from HTN, and one each from diabetes, systemic lupus erythermatosis, and chronic glomerulonephritis. Patients were dialyzed for 219 ± 22 minutes on polysulfone dialyzers with a blood flow rate of 320 ± 42 ml/min and a clearance of 219 ± 22 ml/min (Fresenius F8 or F80). Five of the patients had a primary arterio-venous fistula, and three had a PTFE graft. All patients had well functioning accesses (recirculation 0.55 ± 1.00% range 0 to 4.41%).

Measured parameters

The measured urea removal and actual SRI are shown in Figure 1, grouped according to the individual patients. The mean net urea removal was 18.2 ± 6.8 g/session. The measured SRI (obtained by DDQ) was 64.5 ± 4.0% (mean ± SD) in seven adequately dialyzed patients, and 51.6% in a uremic patient (Fig. 1, patient 7). Table 1 compares the SRI with the equilibrium Kt/V calculated from the equilibrium BUN (corrected for urea generation during the rebound period). The coefficient of variation of equilibrium Kt/V averaged 71% greater than that of SRI, because of the nonlinear relationship between Kt/V and SRI (Fig. 9). Figure 2 shows the measured post-dialysis urea distribution volumes and urea generation rates. The individual patient coefficient of variation for the urea distribution volume ranged from 2.8% to 7.4%; Table 1).

Accuracy of absolute urea removal by different kinetic models

We compared the estimated urea removal predicted by the kinetic methods to the actual urea removal determined by dialysate collection (Fig. 3). The 1-pool model significantly overestimated absolute urea removal by 7.0 ± 4.4% ($P < 0.001$); absolute urea removal was overestimated in 28 of 32 sessions. The 2-pool model accurately estimated absolute urea removal. Indeed, urea removal was overestimated in only 3 of 32 sessions, and on average slightly underestimated urea removal (2.1 ± 4.1%, $P = 0.047$, Figs. 4). While the mean absolute urea removal estimated by the Smye formula was close to the actual urea removal (Fig. 3), the large SD of 23.9% indicates that it imprecisely estimates absolute urea removal. The equilibrium BUN predicted by the Smye method is very close to the measured equilibrium BUN (Fig. 5), suggesting that the Smye method does not calculate an accurate V (data not shown).

Accuracy of SRI estimated by different kinetic models

Estimation of the absolute urea removal depends on a accurate estimate of the urea distribution volume, which is poorly estimated as 0.58 · body wt by the Smye formula, and not considered in the URR and Daugirdas methods. Therefore, we calculated the estimated SRI (net urea removed as a fraction of the pre-dialysis urea content of the body), since this parameter should be less sensitive to errors in the estimation of urea distribution volume (Fig. 6). We found that the urea reduction ratio systematically overestimated SRI in almost all dialysis sessions by 5.6 ± 4.2% ($P < 0.001$, Figs. 6 and 7). The one pool model significantly overestimated SRI by 7 ± 4.4% ($P < 0.001$), whereas the 2-pool and Smye methods estimated SRI more closely (Fig. 6). The individual patient coefficient of variations are shown in Table 2.

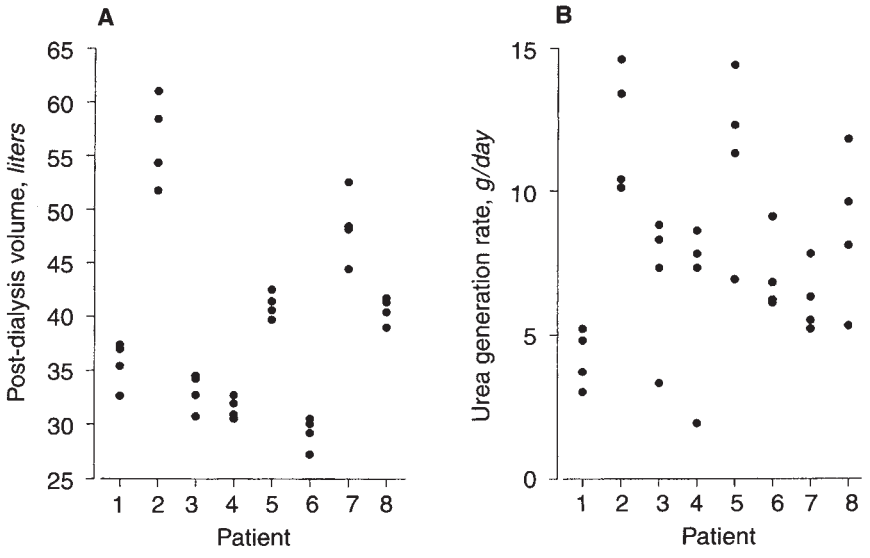

Fig. 2. *(A) End dialysis urea distribution volume and (B) urea generation rate in individual dialysis sessions.* Urea distribution volume calculated from direct dialysate collection and equilibrium BUN obtained one hour post-dialysis using equation 3. Urea generation rate calculated from one hour BUN and BUN obtained before next dialysis using equation 4. Data displayed as in Figure 1.

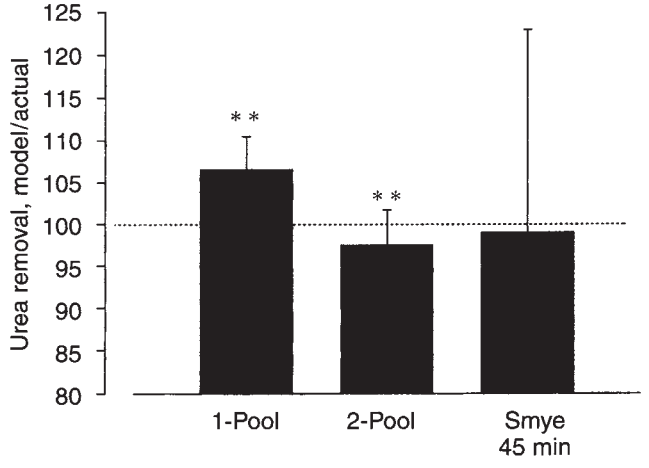

Fig. 3. *Predictive accuracy of absolute urea removal estimated by blood-side kinetic models.*

The SRI estimated by each of the methods had a high correlation with the actual SRI, although the URR method systematically overestimated SRI. The Smye method was slightly better than the 2-pool model and predicted the equilibrium BUN very accurately (Figs. 6 and 7). The Smye method using an intradialytic sample at 45 minutes performed slightly better than when the intradialytic sample was taken at 90 minutes. The Smye method also had a high correlation when analyzed using Kt/V ($r = 0.913$ at 45 min; 0.857 at 90 min). Again, the 45 minute value was slightly more accurate. The Daugirdas method predicted SRI quite accurately ($-1.0 \pm 5.2\%$, $P > 0.05$) with a correlation coefficient of 0.868 (Figs. 6 and 7).

Urea mass transfer coefficient. The two pool model more accurately estimated both absolute and relative urea removal than the 1 pool model, suggesting that urea does not follow 1 pool urea kinetics, and hence, that the urea K_c is important in determining the amount of urea removed from the body. Figure 8 shows the calculated urea K_c for each dialysis session, arranged by individual patient. The mean urea K_c was 695 ± 370 ml/min. Normalizing to an average urea distribution volume of 40 liters ($K_c/V \cdot 40$) only slightly reduced the variation in urea K_c to 690 ± 253 ml/min. The urea K_c coefficient of variation varied from 12.7 to 38.7 with a mean of 22.6 ± 7.8. This suggests that the urea K_c varies by 22% from session to session.

Discussion

There is general agreement that the dose of dialysis is better quantitated by direct measurement of urea removal than any blood-side kinetic method [2, 3, 15], because the direct measurement circumvents errors caused by compartment/blood pool effects, improper calibration of blood pumps, etc. This has been directly studied in the early 1980's by Malchesky et al and Ellis et al [20, 21]. Recently, real-time devices have been developed to measure dialysate urea concentration and flow [16, 22–24]. A recent multi-center trial has validated that an on-line monitor can adequately measure urea removal, and hence dialysis adequacy [16]. Hence, direct dialysate collection can serve as a gold standard against which to test other schemes to quantitate dialysis. However, dialysate quantitation, either by tanks or on-line measurement, is difficult or costly. Therefore, we analyzed the ability of several blood-side measurement schemes to accurately measure either absolute or fractional urea removal. We express the fractional urea removal in terms of SRI, the *net* urea removal expressed as a fraction of total body urea content. SRI can be related to the more conventional Kt/V as shown in Figure 9.

The results of this study are important for three reasons: (1) we found unexpectedly large variations in SRI between sessions despite similar dialysis prescriptions; (2) we show that blood side kinetic modeling can accurately predict urea removal; (3) we show that both the Smye and Daugirdas methods, attractive because of their simplicity, can accurately predict SRI, and that the timing of the extra point in the Smye method is not critical. These observations, along with their clinical significance, are discussed below.

Session to session variability

We accurately measured UGR using the change in BUN from the equilibrium state one hour after dialysis to the pre-dialysis

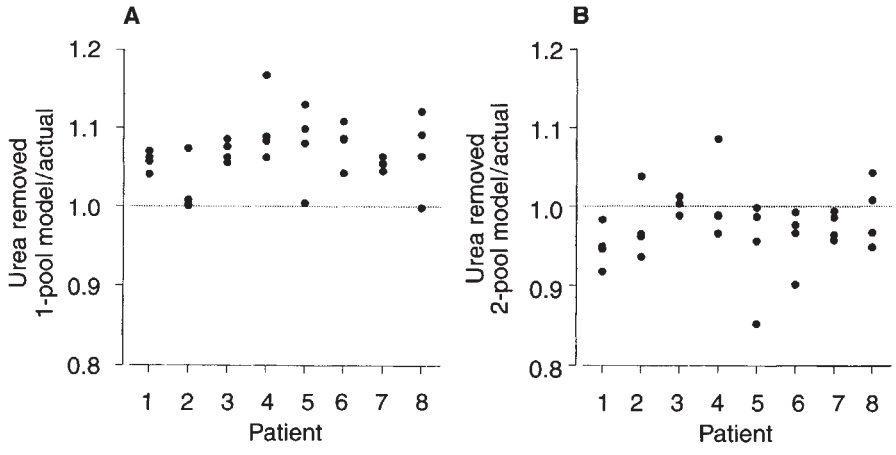

Fig. 4. *Predictive accuracy of absolute urea removal estimated by one and two pool models.* Data from individual dialysis sessions displayed as in Figure 1.

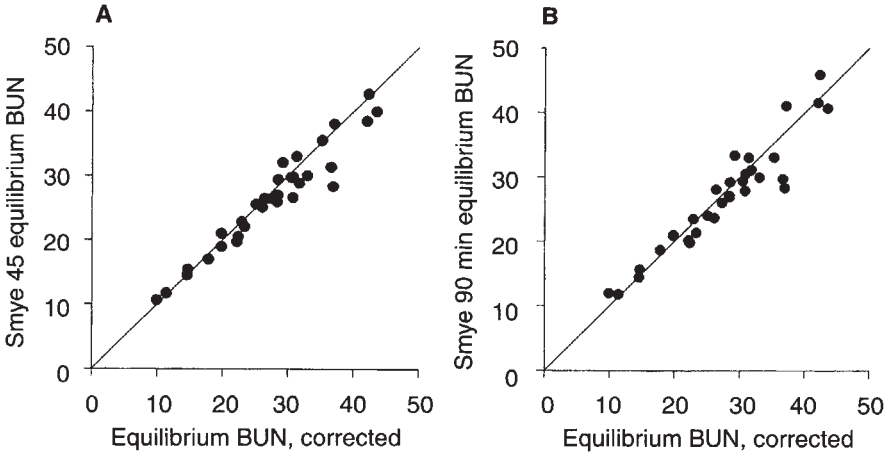

Fig. 5. *Accuracy of estimated equilibrium BUN by Smye methods.* (**A**) Smye 45 minute equilibrium BUN (r = 0.966). (**B**) Smye 90 minute equilibrium BUN (r = 0.950). Solid line is line of identity.

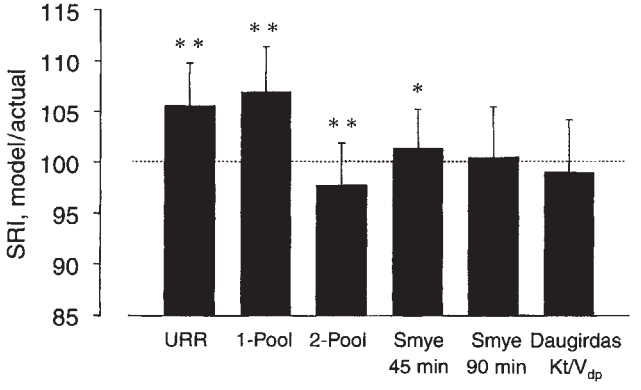

Fig. 6. *Predictive accuracy of SRI estimated by blood-side kinetic models.*

BUN 48 or 72 hours later. This method does not overestimate UGR, as in previous studies, because it is not affected by the post-dialysis rebound in urea concentration. We found a large variation in urea generation rate measured after four different dialysis sessions. This result was expected, since UGR is primarily influenced by the patient's dietary intake, which may vary substantially from day to day.

However, despite the use of constant dialysis prescriptions (such as blood flow rate, dialysis membrane, and dialysis time), we also found a substantial session to session variability in SRI (Table 1, Fig. 1). This is the first report of such variability in SRI, to our knowledge. The absolute urea removal will be influenced by the initial BUN, which varies according to the UGR and interval from last dialysis. In contrast, the variability in SRI, which should be constant, suggests that a patient-centered parameter varied from session to session. Some of the variability may be accounted for by small variations in blood pump speed. While we kept the blood pump speed constant, it is conceivable that the actual blood flow rate varied from session to session because of changes in the pre-pump pressure, which was not recorded. Blood pumps were calibrated at −100 mm Hg, which could be different from the pre-pump pressures present during the dialysis sessions. Some of the session to session variation in SRI can be accounted for by session to session variability in the urea mass transfer coefficient (K_c, Fig. 8). K_c did vary from patient to patient, as previously [1, 8], although the session to session K_c was much smaller than in previous studies [8]. We are not certain of the cause of the different findings between the two studies, although we suspect that part of the difference is caused by the more accurate measurement of total body water in the present study. Whether this is the only explanation is uncertain, especially considering the accuracy of the Daugirdas formula, which does not consider any patient-centered parameters (see below).

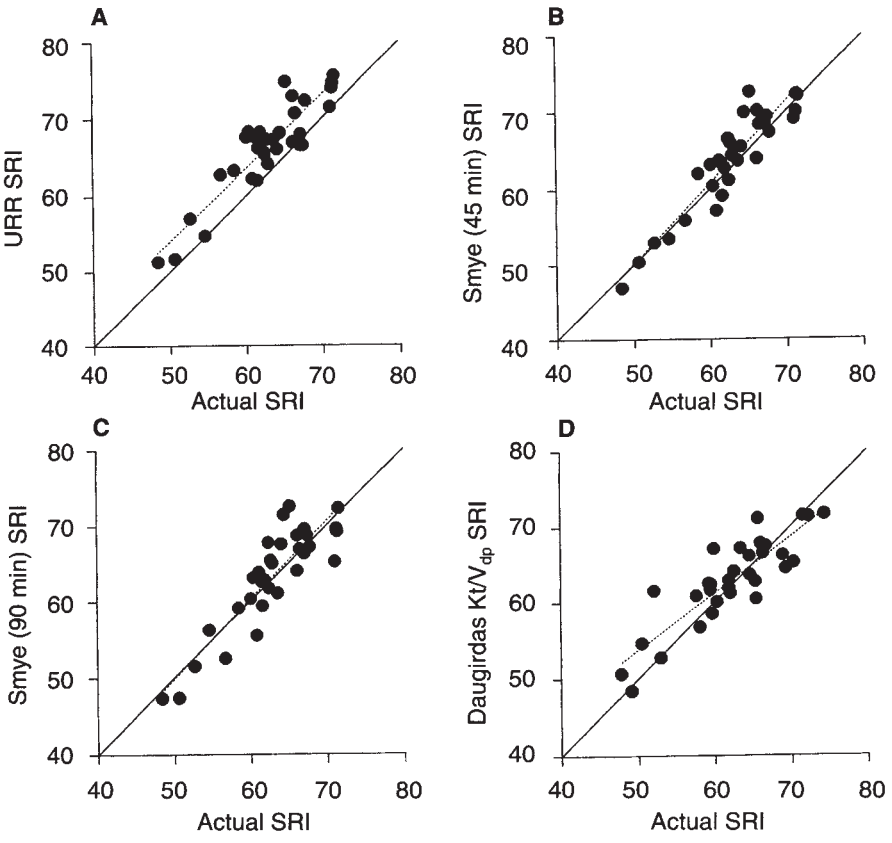

Fig. 7. *Correlation between predicted and actual SRI for kinetic models.* (**A**) *2-pool model* (r = 0.910). (**B**) Smye model with interdialytic sample at 45 minutes (r = 0.930). (**C**) Smye model with interdialytic sample at 90 minutes (r = 0.887). (**D**) Daugirdas method of correcting single pool Kt/V to obtain double pool Kt/V (Kt/V_{dp}) (r = 0.867). Solid lines are lines of identity, dashed lines are calculated by least squares regression. $^{*}P < 0.05$; $^{**}P < 0.001$.

Table 2. Coefficient of variation of post-dialysis urea distribution volume and SRI for individual patients over four dialysis sessions

Patient	Post-dialysis volume	Actual SRI	2-Pool SRI	Smye 45 SRI	Smye 90 SRI	Daugirdas SRI
1	6.13	2.51	2.81	1.54	4.06	5.09
2	7.38	4.12	4.46	1.85	3.93	4.56
3	5.27	2.17	1.19	4.63	5.54	5.74
4	3.25	4.10	5.31	4.18	5.87	3.67
5	2.88	5.06	7.02	2.90	6.08	2.88
6	4.79	1.67	4.16	3.16	2.30	2.98
7	6.80	5.14	1.80	1.68	3.91	4.56
8	2.78	2.42	4.23	5.76	5.02	7.70
Mean	5.28	3.40	3.87	3.21	4.58	4.64
SD	1.72	1.37	1.89	1.53	1.27	1.58

Blood side modeling can accurately predict urea removal

We found that the 1-pool model, despite being given an accurate volume and urea generation rate, cannot accurately predict either absolute urea removal or SRI. It consistently overestimates urea removal by about 7%. Because blood urea falls more rapidly during dialysis than predicted from the 1-pool model, it would be expected that a 1-pool model should overestimate urea removal. Our direct measurements show that this is indeed true. Similarly, the urea reduction ratio also was unable to accurately predict SRI, and thus is also an unacceptable method for monitoring dialysis delivery as recently suggested by others [25].

In contrast, we found that a simplified 2-pool model can more accurately estimate both absolute urea removal and SRI during hemodialysis. This suggests that urea kinetics during dialysis more closely follow double pool rather than single pool kinetics during high flux hemodialysis. Unfortunately, this accuracy in estimation was achieved at a cost: namely, that the 2-pool model had to be provided with an accurate volume. Obtaining an accurate volume is difficult. The volume calculated by single pool methods typically achieve coefficients of variation of about 10% or greater. Indeed, measurement of volume by direct dialysate quantification of urea still had an coefficient of variation of 3 to 7%.

There has been substantial debate in the dialysis literature about the mathematical adequacy of 2-pool kinetic modeling. The observation that urea falls rapidly during the first few minutes of dialysis, and rebounds substantially within two minutes have been taken as evidence to support a blood pool model which incorporates the effect of cardiopulmonary circulation. According to this theory, urea-poor blood returning from the venous limb of the access is rapidly pumped into the arterial circulation, and thence to the arterial side of the access, thus bypassing all tissue compartments/pools. From a kinetic modeling point of view, this introduces several new parameters, all of which are difficult to measure clinically. The results of our study show that the 2-pool model, while not totally accurate in the first and last few minutes of dialysis, is sufficiently accurate for routine clinical use, at least for estimating urea removal.

The Smye method is accurate

The Smye method was introduced in 1992 for use in children. In the original description of the model, no attempt was made to validate the accuracy. We found that the Smye method accurately

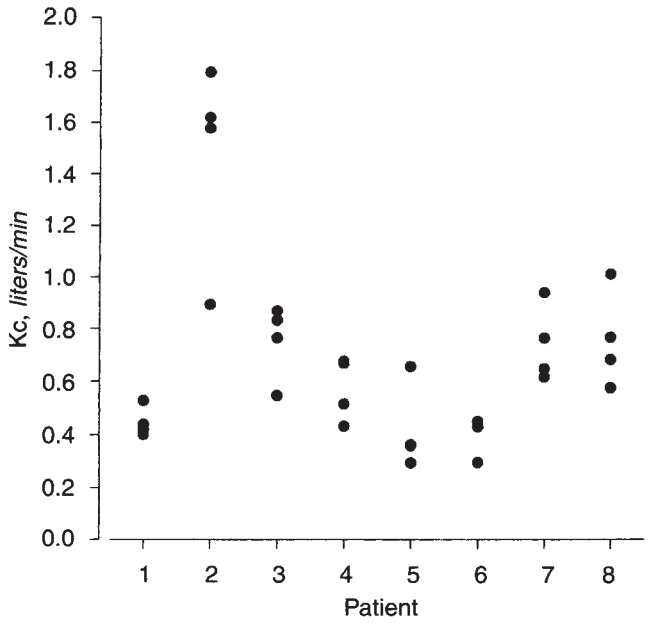

Fig. 8. *Urea mass transfer coefficients (K_c) derived from 2-pool model.* Data from individual dialysis sessions are displayed as in Figure 1.

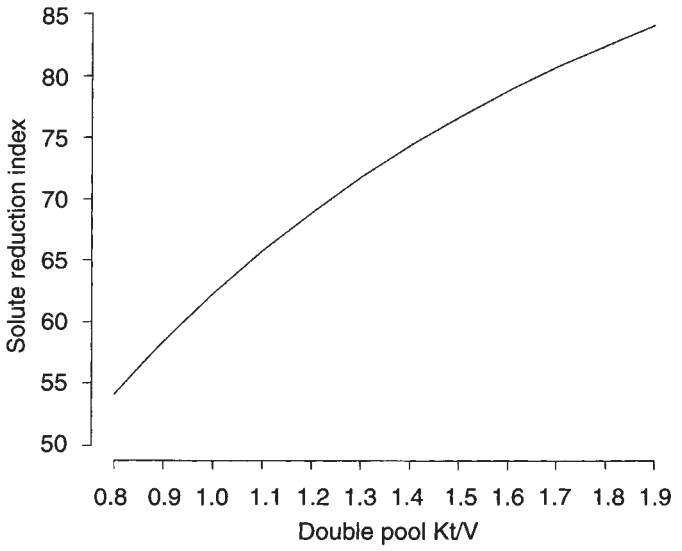

Fig. 9. *Conversion between double pool Kt/V and SRI.* Data are calculated using equation 12, assuming UGR 8 g/day, Td three hours, predialysis BUN 70 mg%, predialysis V 42 liters.

predicted the SRI, although it was unable to estimate accurately the absolute urea removal, unless provided with the correct volume (data not shown). In contrast to the amount of data needed for the 2-pool model, the Smye method requires only one additional sample. Furthermore, we showed that the timing of this sample was not critical; nearly similar accuracy was obtained when samples were taken at 45 minutes or 90 minutes. Our data show a slight preference for the intradialytic sample to be drawn at 45 minutes, although the difference is not large. This has profound clinical implications, since it is often difficult to obtain exactly timed intradialytic samples under routine operating conditions. In contrast, it is not difficult to get samples drawn, as long as the time is written down on the sample. The improved predictive accuracy of the Smye method over the 1-pool model suggests that the Smye method incorporates a more accurate description of urea kinetics than the 1-pool model.

The Daugirdas formula is accurate

Daugirdas noticed that the single pool Kt/V overestimates the actual double pool Kt/V by an amount which is proportional to the rate of dialysis (K/V). He devised a simple method which corrects the single pool Kt/V for so-called 'double pool' effects, yielding an estimate of the double pool Kt/V (equation 11) [19]. We found that use of this simple correction factor is able to substantially reduce the mean error in estimated SRI from 7% (for single pool Kt/V, Fig. 4) to −1%. The Daugirdas correction has a similar correlation coefficient as the Smye method for predicting SRI. This result was unexpected for several reasons. First, all the other methods which use only pre- and post-dialysis samples to estimate urea kinetics (URR, 1-pool model) are not accurate. Second, the Daugirdas correction does not allow for patient to patient or session to session variation in urea kinetics. Both the 2-pool model and Smye method calculate a urea mass transfer coefficient, which varies among patients and from session to session (Fig. 8). That the Daugirdas correction is so accurate suggests that most of the inaccuracy in the 1-pool model is related to the speed of dialysis relative to some intrinsic resistance to urea removal. The residual error in predicted SRI which remains after the Daugirdas correction may be related to variations among patients or sessions or both.

Conclusions

We conclude that the 1-pool model consistently overestimates urea removal and SRI, which leads to inappropriately short dialysis times. The 1-pool model should not be used for dialysis quantitation during fast dialysis. The 2-pool model slightly underestimates absolute urea removal and SRI, but cannot be recommended because it requires an accurate total body water which is difficult to obtain clinically. The Smye and Daugirdas methods can accurately measure SRI, and are sufficiently accurate to measure SRI in clinical settings. Given the extreme simplicity of the Daugirdas correction to the single pool Kt/V (equation 11), we propose that it be tested as an index of dialysis adequacy in a randomized-controlled trial to monitor of the amount of hemodialysis delivered to the patient. We also propose that dialysis dose be expressed as fractional net urea removal (SRI) rather than Kt/V because the former is easier to comprehend, and shifts the focus from the dialyzer (Kt/V kinetics) back to the patient (SRI). These proposals will be tested in the upcoming NIH-sponsored HEMO study.

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Appendix A. Calculations

Dialyzer urea dialysance:

$$PFR = BFR * [(1 - HCT) * Fw + HCT * 0.7] \quad (1)$$

$$Dialysance = PFR * \frac{(C_{inlet} - C_{venous})}{C_{inlet}} + UF * \frac{C_{venous}}{C_{inlet}}$$

Access recirculation:

$$Recirculation = \left(1 - \frac{C_{Arterial} - C_{Venous}}{C_{Occluded\ Arterial} - C_{Venous}}\right) * 100 \quad (2)$$

Urea distribution volume at end of dialysis:

$$V_{Td} = \frac{\text{Net Urea Removed} - C_0 * UF}{C_0 - C_{eq}^{corr}} \quad (3)$$

$$V_0 = V_{Td} + UF$$

Urea generation rate:

$$UGR = \frac{(V_{Td} + \text{Wt Gain}_{interdialytic}) * C_{48} - V_{Td} * C_{equil}}{(48 - T_{eq})} \quad (4)$$

Equations 3 and 4 were solved iteratively until a stable solution was found (generally in 2 to 4 iterations).

Actual SRI from dialysate urea:

$$SRI_{actual} = \left(\frac{\text{Urea Removed} - UGR * Td}{C_0 * V_0}\right) * 100 \quad (5)$$

Single pool Kt/V estimated by second generation logarithmic estimate by method of Daugirdas [18]:

$$Kt/V = -\ln(R - 0.008 * t) + (4 - 3.5 * R) * UF/W \quad (6)$$

$$R = \frac{C_0}{C_{Td}}$$

The equilibrium Kt/V was calculated using equation 6, but replacing C_{Td} with the equilibrium BUN (C_{equil}^{corr}, corrected for urea generation during the rebound phase).

SRI estimated from the urea reduction ratio:

$$SRI_{URR} = URR = 100 * \left(1 - \frac{C_{Td}}{C_0}\right) \quad (7)$$

SRI estimated by the 1-pool model:

$$SR_{1\text{-}pool} = \left(1 - \frac{C_{Td} * V_{Td}}{C_0 * V_0}\right) * 100 \quad (8)$$

SRI estimated by the 2-pool model:

$$SRI_{2\text{-}pool} = \left(1 - \frac{C_{Td}^{cell} * V_{Td}^{cell} + C_{Td}^{ecf} * V_{Td}^{ecf}}{C_0 * V_0}\right) * 100 \quad (9)$$

SRI estimated by Smye model:

$$SRI_{Smye} = \left(1 - \frac{C_{Smye}^{corr} * V_{post}}{C_0 * V_0}\right) * 100 \quad (10)$$

Double pool Kt/V (Kt/V_{dp}) estimated from single pool Kt/V using the Daugirdas correction [19]:

$$Kt/V_{dp} = Kt/V * \left(1 - \frac{0.6}{Td/60}\right) + 0.03 \quad (11)$$

SRI estimated from double pool Kt/V, corrected for urea generation during dialysis:

$$SRI_{Daugirdas} = \left(1 - \exp(-Kt/V_{dp}) - \frac{UGR * Td}{C_0 * V_0}\right) * 100 \quad (12)$$

This estimation ignores the effect of volume loss during dialysis.

Appendix B. Two-pool mathematical model of hemodialysis

The two-pool variable volume model incorporates differential equations which describe the movement of urea, water, and another solute (X) from cell to ECF to the dialyzer. During dialysis, urea diffuses from cell to ECF, and is removed by diffusion and convection across the dialyzer. Urea is constantly generated in the liver, and assumed to directly enter the ECF [26]. For the purpose of the model, all impermeant non-urea solutes (NaCl, KCl, mannitol, etc.) are lumped together as a single solute (X). The model consists of six differential equations describing mass balances for cell and ECF urea, cell and ECF solute X, and cell and ECF volume as a function of time. This formulation is similar, but not identical, to that of Abbrecht and Prodany [27], Heinekin et al [6], and Pastin and Colton [28].

Two differential equations describe the conservation of volume in the cell (V^{cell}) and ECF (V^{ecf}):

$$\frac{d}{dt} V^{cell} = -J_v^{memb}$$

$$\frac{d}{dt} V^{ecf} = J^{memb} - J_v^{dial} \quad (13)$$

where J_v^{memb} and J_v^{dial} are the transmembrane water flow out of the cell and into the dialyzer. Flux greater than zero indicates flow from cell to ECF or ECF to dialyzer.

Four differential equations describe the conservation of urea (i = 1) and X (i = 2) in the cell and ECF compartment:

$$\frac{d}{dt}(V^{ecf} C_i^{ecf}) = -J_i^{memb} + UGR_i + GFR\, C_i^{ecf}$$

$$\frac{d}{dt}(V^{cell} C_i^{cell}) = J_i^{memb} - J_i^{dial} \quad (14)$$

where C_i^j is the concentration of solute i in compartment j, and J_i^j is the transmembrane flux of solute i across membrane j. UGR is the urea generation rate (only for urea), and GRF is the glomerular filtration rate. We assume that X is impermeable to cells, so J_2^{memb} is zero.

Standard equations taken from non-equilibrium thermodynamics are used to describe the transmembrane transport of solute and solvent. Since the reflection coefficient for urea is one [29–31], urea moves only by diffusion, and not by solvent drag. The equations for flux across the cell membrane are:

$$J_v^{memb} = P_f^j \sum_{i=1}^{2} [\gamma_i (C_i^{cell} - C_i^j)]$$

$$J_v^{memb} = P_i^j (C_i^j - C_i^{cell}) \quad (15)$$

where P_f^j and P_i^j are the mass transfer coefficients of water and the i^{th} solute, and γ_i is the osmotic coefficient of solute i. The values for γ are 1.846 for X and 0.96 for urea [32, 33].

$$J_v^{dial} = Q_F$$

$$J_u^{dial} = D_u((1 - Q_F/Q_B) + Q_F) C_u^{ecf}$$

$$J_x^{dial} = D_{Na}(1 - Q_F/Q_{PW})(C_x^{dial} - C_x^{ecf}) - Q_F \alpha_x C_x^{ecf} \quad (16)$$

The final equations describe the flux of water, urea and sodium from ECF to dialysate: where Q_F, Q_{BFR}, and Q_{PFR} are the ultrafiltration rate, blood flow rate, and plasma flow rate; α_X is the dialyzer sodium Donnan ratio (0.94) [34]. The TBW and UGR were calculated per equations 5 and 6. ECF volume was estimated as 25% of the initial total body water [9]. The system of six differential equations with initial conditions describing the initial cell and ECF volume, urea and X concentrations was solved using Gear's method (DIVPAG subroutine, IMSL; Houston, TX, USA) for numerically stiff problems on a personal computer (IBM-compatible 486 operating at 33 MHz). The model was written in Microsoft FORTRAN, with a 'user friendly' front end written in Microsoft Quick BASIC.

Appendix C. Abbreviations

BFR, blood flow rate; BUN, blood urea nitrogen; C_x, BUN at time x or location x as appropriate; C^y, BUN at location y or corrected for urea generation (corr); DDQ, direct dialysis quantification; equil, equilibrium sample taken at Td + one hour; Fw, water content of plasma; HCT, hematocrit fraction; J, flux; K_c, urea mass transfer coefficient; Kt/V, single pool Kt/V; Kt/V_{dp}, double pool Kt/V; PFR, plasma flow rate; SRI, solute reduction index; t or Td, dialysis time; V, volume; TBW, total body water; UF, ultrafiltration rate; UGR, urea generation rate; URR, urea reduction ratio.

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