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Comparison of methods to predict equilibrated Kt/V in the HEMO Pilot Study

HEMO Study Group,[1] Prepared by John T. Daugirdas, Thomas A. Depner, Frank A. Gotch, Tom Greene, Prakash Keshaviah, Nathan W. Levin, and Gerald Schulman

National Institutes of Health, NIDDK, Bethesda, Maryland

Comparison of methods to predict equilibrated Kt/V in the HEMO Pilot Study. The ongoing HEMO Study, a National Institutes of Health (NIH) sponsored multicenter trial to test the effects of dialysis dosage and membrane flux on morbidity and mortality, was preceded by a Pilot Study (called the MMHD Pilot Study) designed to test the reliability of methods for quantifying hemodialysis. Dialysis dose was defined by the fractional urea clearance per dialysis determined by the predialysis BUN and the equilibrated postdialysis BUN after urea rebound is completed (eKt/V). In the Pilot Study the blood side standard for eKt/V was calculated from the predialysis, postdialysis, and 30-minute postdialysis BUN. Four techniques of approximating eKt/V that eliminated the requirement for the 30-minute postdialysis sample were also evaluated. The first adjusted the single compartment Kt/V using a linear equation with slope based on the relative rate of solute removal (K/V) to predict eKt/V (rate method). The second and third techniques used equations or mathematical curve fitting algorithms to fit data that included one or more samples drawn during dialysis (intradialysis methods). The fourth technique (dialysate-side) predicted eKt/V from an analysis of the time-dependent profile of dialysate urea nitrogen concentrations (BioStat method; Baxter Healthcare, Inc., Round Lake, IL, USA). The Pilot Study demonstrated the feasibility of conventional and high dose targets of about 1.0 and 1.4 for eKt/V. Based on the blood side standard method, the mean ± SD eKt/V for patients randomized to these targets was 1.14 ± 0.11 and 1.52 ± 0.15 (N = 19 and 16 patients, respectively). Single-pool Kt/Vs were about 0.2 Kt/V units higher. Results were similar when eKt/V was based on dialysate side measurements: 1.10 ± 0.11 and 1.50 ± 0.11. The approximations of eKt/V by the three blood side methods that eliminated the delayed 30-minute post-dialysis sample correlated well with eKt/V from the standard blood side method: r = 0.78 and 0.76 for the single-sample (Smye) and multiple-sample intradialysis methods (N = 295 and 229 sessions, respectively) and 0.85 for the rate method (N = 295). The median absolute difference between eKt/V computed using the standard blood side method and eKt/V from the four other methods ranged from 0.064 to 0.097, with the smallest difference (and hence best accuracy) for the rate method. The results suggest that, in a dialysis patient population selected for ability to achieve an equilibrated Kt/V of about 1.45 in less than a 4.5 hour period, use of the pre and postdialysis samples and a kinetically derived rate equation gives reasonably good prediction of equilibrated Kt/V. Addition of one or more intradialytic samples does not appear to increase accuracy of predicting the equilibrated Kt/V in the majority of patients. A method based on dialysate urea analysis and curve-fitting yields results for equilibrated Kt/V that are similar to those obtained using exclusively blood-based techniques of kinetic modeling.

End-stage renal disease (ESRD) is a critically important health care problem in the United States. Despite advances in the prevention and treatment of renal disease, the size of the ESRD program continues to increase. The majority of patients with ESRD are treated by hemodialysis. The gross mortality rate among dialysis patients is 23% per year [1], despite long experience with treatment and improvement in technical aspects of the dialysis procedure. In an attempt to establish interventions to improve survival of hemodialysis patients, the United States National Institutes of Health has sponsored the HEMO Study, which is now ongoing. This is a multicenter, prospective, randomized trial designed to assess the effect of hemodialysis dose and flux on morbidity and mortality. One primary hypothesis to be tested in the study is that a higher dose of dialysis [urea reduction ratio (URR) in the range of 75%, single pool Kt/V of about 1.65, equilibrated Kt/V of 1.45] may reduce morbidity and/or mortality as compared to a standard amount of dialysis (URR of about 67%, a single-pool Kt/V of about 1.25, equilibrated Kt/V of 1.05.) The second primary hypothesis to be tested is that the use of high flux membranes may reduce morbidity and/or mortality.

The HEMO Study was preceded by a Pilot Study, the MMHD (Mortality and Morbidity in Hemodialysis) Study, among the purposes of which was the evaluation of various methods of assessing urea removal during hemodialysis. Of greatest concern was the rebound in urea concentration at the end of the treatment. Rebound is due to the non-uniform distribution of urea and other solutes among various body compartments that develops during dialysis and reflects diminished solute removal during dialysis. Any technique that is proposed to quantify dialysis accurately must include the rebound component. At the time the Pilot Study was launched, data were available suggesting that post-dialysis urea rebound may be highly variable among patients, and even within the same patient from treatment to treatment [2, 3]. To insure accuracy, direct measurement of the post-dialysis equilibrated BUN (measured after rebound was largely complete)

[1] The institutions and investigators who participated in the Hemodialysis (HEMO) Pilot Study are: Garabed Eknoyan (Baylor College of Medicine), Joel Kopple (Harbor/UCLA), Andrew Levey (New England Medical Center), Nathan Levin (Beth Israel Medical Center), Gerald Schulman (Vanderbilt University Medical Center), Gerald Beck (Data Coordinating Center, Cleveland Clinic Foundation), and John Kusek, (NIDDK Project Officer).

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Table 1. Pilot Study Urea Kinetic Modeling

	Baseline		Follow-up	
	Usual Rx	Target eKt/V 1.4	Target eKt/V 1.0	Target eKt/V 1.4
N of dialyses	144	87	35	29
N of patients	48	46	19	16
Qb *ml/min*	391 (43)	415 (45)	297 (65)	403 (57)
Kd *ml/min*	245 (27)	273 (28)	213 (18)	259 (25)
t *min*	210 (27)	219 (29)	206 (32)	232 (30)
Urea volumes *liter*				
(a) Single-pool	35.1 (6.4)	37.4 (8.1)	34.3 (7.6)	35.5 (6.0)
(b) Anthropometric	35.9 (7.1)	36.3 (6.9)	36.3 (7.8)	36.6 (5.4)
ratio of a/b	0.99 (0.14)	1.03 (0.12)	0.95 (0.14)	0.97 (0.11)
Kt/V measures				
(a) Single-pool	1.50 (0.21)	1.64 (0.24)	1.32 (0.11)	1.70 (0.18)
(b) True equilibrium, eKt/V[a]	1.28 (0.19)	1.42 (0.23)	1.14 (0.11)	1.52 (0.15)
(c) BioStat	1.33 (0.23)	1.44 (0.20)	1.10 (0.11)	1.50 (0.11)
(d) a − b	0.217 (0.099)	0.229 (0.147)	0.177 (0.096)	0.184 (0.132)
(e) 0.6K/V − 0.03 (Rate Eq)	0.231 (0.051)	0.245 (0.057)	0.205 (0.045)	0.240 (0.046)
(f) d − e	−0.014 (0.089)	−0.016 (0.142)	−0.029 (0.080)	−0.055 (0.099)

Data are mean ± SD. The data are summarized on a patient basis; that is, the means and standard deviations are provided for the average values of the kinetic parameters computed for each patient during each of the indicated periods of the study.

[a] Computed using the 2-pool model with the 30 minute post-BUN

was considered necessary. Because of the impracticality of waiting for equilibration to occur (30 to 60 min post-dialysis) for routine urea kinetic modeling, a method was sought to approximate this value that could be carried out in large numbers of patients in multiple dialysis centers. Methods chosen were based on double-pool mathematical approximation of the equilibrated dose of dialysis (eKt/V-urea) derived from changes in blood urea concentration during dialysis, or from changes in dialysate urea concentration. Three blood side methods and a dialysate-side method were selected for comparison with results obtained from direct measurement of the equilibrated BUN. To accomplish this goal, four pilot centers were selected in which detailed urea kinetic analyses were performed in relatively small numbers of patients.

METHODS

Pre-Pilot Study

A Pre-Pilot Study was carried out in three of the HEMO Pilot Study Clinical Centers (Beth Israel Medical Center, New England Medical Center, and Vanderbilt University) to assess kinetic modeling methods prior to initiation of the Pilot Study. Two dialyses in each of 22 patients and a single dialysis in four additional patients were modeled, for a total of 48 modeled dialyses. Blood samples for determination of serum urea nitrogen (BUN) were drawn predialysis, at 70 minutes into dialysis, immediately post-dialysis, and at 2, 5, 10, 15, 20 and 30 minutes post-dialysis. To minimize the dilutional effects of potential access recirculation, the sample obtained during dialysis as well as the immediate post-dialysis sample were drawn from the arterial line sampling port after the blood flow had been reduced to 100 ml/min for approximately 10 seconds.

Pilot Study

The Pilot Study was carried out at four Clinical Centers (Beth Israel, Harbor Medical Center; University of Southern California; New England Medical Center; and Vanderbilt University). The purposes of the Pilot Study were to test the feasibility of the protocol, evaluate the adequacy of the data entry forms, and to provide additional data with which to select the method for quantitating dialysis during the Full-Scale Study. A total of 49 patients were enrolled of which 24 were diabetic, 20 were female, and 24 were Caucasian.

After enrollment each patient remained on his or her usual dialysis prescription for approximately three weeks, during which urea kinetics were modeled for three to four dialysis sessions. Subsequently, urea modeling was done during at least two additional baseline dialyses at a target equilibrated Kt/V of 1.4 based on dialysis prescriptions provided by the Data Coordinating Center (Cleveland Clinic Foundation), which were prepared using estimated dialyzer clearances and values for urea distribution volume obtained from the initial modeling studies. A requirement for randomization included achieving an equilibrated Kt/V of at least 1.3 during each of two different modeled dialyses. Thirty-eight of the 49 enrolled patients successfully achieved this goal and were randomized to equilibrated Kt/V goals of either 1.0 or 1.4 per dialysis, after which two additional dialyses were modeled. In the Pilot Study design, an attempt was made to keep the dialysis treatment time similar at the two Kt/V levels; hence, the rate of dialysis, or K/V, differed between the two Kt/V treatment arms. The number of dialysis sessions at each point are listed in Table 1. Of the 49 patients studied, complete baseline data on the usual prescription were available for 144 dialysis sessions in 48 patients. In 46 patients (87 sessions) data were available from the baseline period when trying to achieve the eKt/V goal of 1.4. From the follow-up period, once randomized into the standard and high eKt/V goals, data were available in 19 and 16 patients, from 35 and 29 sessions, respectively.

For the Pilot Study, the set of blood samples drawn during and after dialysis was different than the set drawn during the Pre-Pilot Study. An "immediate" post-dialysis sample was drawn approximately 10 seconds after slowing blood flow to 100 ml/min (as in the Pre-Pilot Study), but only one delayed post-dialysis sample was obtained 30 minutes after stopping dialysis because, as

described under the **Results** section below, the Pre-Pilot Study showed that collection of the six BUN measurements between 2 and 30 minutes after dialysis provided little additional information regarding the equilibrated post-dialysis BUN beyond that provided by the 30 minute sample alone.

In the Pilot Study the pattern of intradialytic samples was also different from the Pre-Pilot Study. During the baseline (pre-randomization) phase of the Pilot Study, blood for BUN was drawn pre-dialysis, 70 minutes into dialysis, and also at 60% and 80% of the total treatment time into dialysis, to attempt to determine the optimum timing of an intradialytic sample. After randomization in the Pilot Study, based on a preliminary analysis of the data, the later intradialytic samples were no longer obtained, and only one intradialytic sample was drawn 70 minutes after the start of dialysis.

BUN was measured in all serum samples at a central laboratory (Spectra Laboratories, Fremont, CA, USA). For the Pilot Study, in addition to the blood sided measures of urea, the BioStat device [4] (Baxter Healthcare, Inc., Deerfield, IL, USA) was used. This instrument measures dialysate urea concentration on line at 5 to 10 minute intervals (using urease and an ammonium-sensitive electrode) throughout the treatment and provides and independent check of delivered dialysis therapy.

Blood side methods for estimating eKt/V

Two-pool model with seven post-dialysis BUNs. With this method, used only during the Pre-Pilot Study, a 2-pool variable volume model of hemodialysis urea kinetics [5–8] was fit to the BUN values measured pre-dialysis, immediately post-dialysis, and at 2, 5, 10, 15, 20 and 30 minutes post-dialysis as follows. For each modeled dialysis, the *in vivo* blood water dialyzer clearance was estimated from the blood and dialysate flows and the *in vitro* dialyzer KoA using standard formulae [9] with appropriate adjustments for blood water concentration [10, 11] and ultrafiltration. The computed dialyzer clearance (Kd), the pre-dialysis BUN, the estimated equilibrated urea generation rate, and the ultrafiltration rate calculated from weight loss during dialysis were then used as inputs along with trial estimates of the intercompartment transfer coefficient (Kc) and total urea volume (V) to numerically solve the 2-pool variable volume model to predict values for the seven postdialysis BUNs. The ratio of the intracellular and extracellular volumes was assumed to be 2 to 1 [6]. To account for rebound due to cardiopulmonary recirculation [12], the model allowed for a change in the predicted BUN between the immediate post-dialysis and the two minute post-dialysis BUN. Optimal values of Kc and V were then derived using numerical methods to produce predicted BUNs with the minimum sum of squared deviations from the actually observed values. Based on the optimal Kc and V, the equilibrated (2 hour) post-dialysis BUN (Ceq) was estimated and corrected for urea generation. This estimate of Ceq was then substituted for the post-dialysis BUN using Depner's 2-BUN algorithm [8] for computing eKt/V. In this application of the 2-BUN method, the pre-dialysis BUN, the estimated Ceq, the modeled urea distribution volume (V), the weight change during dialysis and the duration of dialysis were used as inputs to compute eKt/V.

Two-pool model with 30 minute post-dialysis BUN. A numerical approach similar to the above was used, except that the optimal Kc and V were obtained by fitting the 2-pool variable volume model to the pre-dialysis, immediate post-dialysis (after adjustment for cardiopulmonary recirculation), and the 30 minute post-dialysis BUNs. The immediate post-dialysis BUN (C_t) was adjusted (C_{tadj}) for cardiopulmonary recirculation [12] by:

$$C_{tadj} = C_t/Fcp,$$

$$Fcp = 1/[1 + K_{AC}/(CO - Q_{AC})],$$

where K_{AC} is the access clearance (assumed to be equal to the dialyzer clearance Kd), CO is the cardiac output (determined from anthropometric body surface area multiplied by a presumed population mean cardiac index of 3.0 [13]) and Q_{AC} is the access flow (assumed to be 800 ml/min [14, 15]). One complication of this method is that often there are two solutions giving an exact fit to the observed BUNs: one with V relatively close to the standard single pool volume and Kc between 150 ml/min and + infinity; and the other with V 30% to 50% smaller than the single pool volume and Kc between 10 and 100 ml/min. In the latter solution with the smaller Kc, the total predicted rebound is typically very large and occurs over several hours, with only a small fraction of the rebound occurring by 30 minutes post-dialysis. Due to its greater biological plausibility and close correlation with the 2-pool model with seven post-dialysis BUNs from the Pre-Pilot Study, the solution with the larger Kc was used in the analyses reported here.

Methods not requiring delayed post-dialysis sampling

Rate adjustment method. The rate adjustment method [16] is based on a regional blood flow model. It predicts that the magnitude of post-dialysis urea rebound is related to the rate of dialysis or dialysis efficiency (K/V). The rate equation predicts the equilibrated Kt/V from the rate of dialysis (K/V) and the single-pool Kt/V (spKt/V). The equation used was:

$$eKt/V = spKt/V - 0.6 \times (spKt/V)/hours + 0.03$$

The spKt/V was computed from the Depner 2-BUN equations [8] using an estimated Kd as described above. The equilibrated Kt/V was then computed from the spKt/V and the duration of dialysis.

Smye method. The Smye method [17, 18] is based on the notion that compartment disequilibrium during dialysis produces a deviation from the expected monoexponential fall in the serum BUN, and the extent of this deviation can be used to predict the equilibrated post-dialysis BUN value. According to Smye and colleagues, the equilibrated postdialysis BUN (Ceq) is defined as:

$$Ceq = C_0 \times \exp[-Td/(Td - 70) \times \log(C_{70}/C_t)]$$

where Td = treatment time, C_{70} is the 70-minute intradialysis BUN, and C_0 and C_t are the pre-dialysis and post-dialysis BUN, respectively. The equilibrated Kt/V was computed from Ceq, the predialysis BUN, and V using the same algorithm used for the other blood-side methods described above.

Two-pool model with three intradialysis BUNs. An approach similar to the 2-pool model with seven post-dialysis BUNs was used, except that the 2-pool variable volume model was fit to the BUNs obtained pre-dialysis, at 70 minutes, at 60% and 80% of the time into dialysis, and immediately post-dialysis. The rationale for the method is that the same factors that cause post-dialysis urea rebound conspire to reduce the intradialytic BUN profile from a monoexponential fall. Making the assumption that the intercompartmental mass transfer coefficient (Kc) is stable during dialysis,

the Kc, and subsequently the post-dialysis urea rebound can be computed from the degree of deviation of the intradialytic BUN profile from a monoexponential decline.

BioStat method. The BioStat device [4] calculates the eKt/V from a double exponential curve fit of the effluent dialysate concentration-time profile. The early, steep slope of the concentration-time profile represents the preferential removal of urea from an easily accessible compartment and the late, shallower slope represents removal from a larger volume of distribution that includes both the easily accessible compartment and a poorly accessible compartment. In a patient with a large dialysis induced concentration disequilibrium between body compartments (hence the large post-dialysis urea rebound), the ratio of the early to late slope is much greater than 1.0. Patients with a small post-dialysis urea rebound have a slope ratio closer to 1, indicating less disequilibrium between the two compartments.

Data analysis

Standards for comparison. For analyses of the Pre-Pilot data, the estimate of eKt/V from the 2-pool model with seven postdialysis BUNs was regarded as the reference standard. For the Pilot Study, the estimate of eKt/V from the 2-pool model with the single 30-minute postdialysis BUN was used as the reference standard, as the Pre-Pilot data indicated that the latter estimate agreed well with the eKt/V derived from the 7 postdialysis BUNs (see Results section, below). In the Pre-Pilot and Pilot studies, respectively, these two methods were used as the standard for comparison with other estimates of eKt/V that were based on intradialysis BUN measurements, the rate equation, or dialysate urea measurements.

Statistical analysis. Comparisons of different estimates of eKt/V were made using the Pearson correlation coefficient (R_P), and the following alternative measures of association or agreement:

(*i*) Spearman correlation coefficient (R_S) [19]: Index of direct association (possibly non-linear) between two methods; less affected by outliers than the Pearson correlation.

(*ii*) Concordance statistic (R_C) [20]: Index of agreement between the methods. It is equal to 1 if there is perfect agreement, and takes on smaller values otherwise. If there is no systematic bias, the concordance statistic is equal to the Pearson correlation; otherwise, the magnitude of the concordance statistic is smaller, as it reflects both association and systematic bias between methods.

(*iii*) Median algebraic difference (median Δ): Median of the differences between eKt/V estimates as computed by two methods. This is an index of systematic bias of one method with respect to the other.

(*iv*) Median absolute difference (median $|\Delta|$): Absolute value of (iii), above. This is an index of agreement between methods.

The bootstrap method [21] with 1,200 independent bootstrap samples was used for statistical comparisons of these measures of agreement between different pairs of estimates of eKt/V. The bootstrap method does not require the assumption of normality, which is violated by several of the measures of agreement considered. The bootstrap approach also allowed us to account for multiple measurements per patient by drawing the bootstrap samples on a patient basis, so that all dialysis sessions for a given patient were jointly included or excluded in each bootstrap sample. The results of these comparisons are described in the footnotes to Tables 2, 3, and 6.

For the Pre-Pilot Study, statistical analyses were restricted to 42 of the 48 modeled dialyses during which all scheduled blood samples were obtained. For the Pilot Study, analyses were restricted to 295 dialyses with complete kinetic modeling data, including a valid BioStat analysis and the pre-dialysis, 70 minute intradialysis, immediate post-dialysis, and 30-minute post-dialysis BUN samples. As noted above, the two additional intradialytic samples (used for the 2-pool model with 3 intradialysis BUNs) were not obtained in the approximately 60 sessions quantified after randomization.

Estimates of eKt/V were compared first for all dialyses and then for individual patients after averaging the results of the three to four modeled dialyses conducted during baseline on the patient's usual prescription. In the Pilot Study analyses, agreement was summarized first for all dialyses and then again after excluding sessions with "deviant" profiles of the BUN or dialysate urea concentrations (see below).

Linear regression analyses were performed to relate $\Delta Kt/V = sp(Kt/V) - eKt/V$ to various dialysis parameters. Mixed effects models [22] with a random coefficient for each patient were used to account for correlations in $\Delta Kt/V$ among dialysis sessions conducted in the same patient.

"Deviant" blood and dialysate profiles defined. A BUN profile was defined as "deviant" if the residual sum of squares for the 2-pool model with the 30-minute postdialysis BUN exceeded 0.01^2 $(mg/dl)^2$. For these BUN profiles the post-dialysis rebound was either too small (or negative) or was too large to be accounted for by the two-pool variable-volume model. Dialysate urea nitrogen profiles that were "deviant" were also treated separately in some analyses. Built into the BioStat is a quality assurance algorithm that rejects concentration measurements that markedly deviate from the predicted concentration-time profile. Urea nitrogen measurements below 3 mg/dl (low limit of the instrument) are also rejected because of inaccuracies in urea nitrogen levels this low. If, in a given dialysis treatment, more than four samples are rejected by this criterion, the run is flagged with the message "Fit Error," indicating an unstable run with significant deviations from the predicted concentration-time profile. Causes for an unstable run include frequent and prolonged machine alarms with dialysate bypass/blood pump shutdown, mid-run changes in dialysis parameters (such as blood flow), vascular access problems, dialyzer clotting, hypotensive episodes, etc. Such "Fit Errors" were treated as "deviant" in a similar fashion to deviant blood sided values.

RESULTS

Prepilot data analysis

Two-pool model with 7 postdialysis BUNs compared to the two-pool model with a 30 minute post-dialysis BUN. In the 42 sessions with complete data, there was excellent agreement between the eKt/V values computed using the 2-pool model with a 30 minute post-dialysis BUN and the eKt/V values computed using the 30 minute post-dialysis BUN plus the additional five BUNs from samples drawn between 0 and 30 minutes post-dialysis. The correlation coefficients were: R_P (Pearson) = 0.985, R_S (Spearman) = 0.975, and R_C (concordance) = 0.984. The median absolute difference between the two eKt/V measures was 0.013 Kt/V units. Thus the Pre-Pilot Study data indicated that the two methods generated similar eKt/Vs. Since the 2-pool model with a single 30 minute post-dialysis BUN is much simpler to

perform, it was used as the reference standard in the subsequent Pilot Study.

Pilot data analyses

Patient characteristics. As shown in Table 1, the mean ± SD delivered Kt/V calculated at baseline using single-pool kinetics was 1.49 ± 0.21. The mean duration of dialysis was 210 ± 27 minutes. The mean single-pool urea distribution volume was 35.1 ± 6.4 liters, with a mean modeled/anthropometric volume ratio of 0.99 ± 0.14. Based on the 2-pool model with the 30 minute post-BUN, (the blood side standard), the delivered equilibrated Kt/V values after randomization were near the target values of 1.0 and 1.4 per dialysis. Although both goals were slightly exceeded at 1.14 ± 0.11 and 1.52 ± 0.15, there was a clear separation of the Kt/V values in the two groups, demonstrating the feasibility of achieving the Kt/V goals of the study.

Accuracy of the various blood-side modeling methods. The true equilibrated Kt/V value obtained from the 2-pool model with the 30 minute post-dialysis BUN is compared with various blood-side estimates in Figures 1 through 3 and in Tables 2 and 3. In Figures 1 through 4, the upper graph shows all modeled sessions (columns A through D in Table 1), including deviant sessions as defined above. The deviant sessions are identified as hollow circles but not excluded from the analysis. The lower graphs in Figures 1 through 4 include only modeled sessions obtained during the baseline period on a constant (the patient's usual) prescription (column A in Table 1). This is necessary as eKt/V results are averaged in the lower graphs on a patient basis, and hence the prescription must be held constant. In all of the lower graphs in Figures 1 through 4, deviant sessions are excluded from the averaging process.

Both the rate equation (Fig. 1) and the two methods based on BUN values during dialysis (Smye method in Fig. 2, and the 2-pool model with 3 intradialysis BUNs in Fig. 3) predicted eKt/V quite well. On an individual dialysis session basis, the rate equation predicted eKt/V significantly better ($P < 0.05$) than the other two blood based methods (Table 2). Averaging across the baseline sessions on the usual prescription improved the accuracy of the Smye method and the 2-pool model with three intradialysis BUNs to a greater extent than than the rate equation method. After averaging, the performance of the three blood side methods was similar, with no statistically significant differences among the methods on any of the indices of agreement considered (Table 3).

The data in the Figures 1 through 3 and Tables 2 and 3 overestimate the ability of the rate equation and intradialytic methods to predict the ΔKt/V (the difference between single pool and equilibrated Kt/V), as they focus on the eKt/V. This is because computed values of eKt/V usually fall within 0.4 Kt/V units of the single-pool Kt/V, regardless of which method is used to estimate eKt/V. Thus, in any data set with a substantial range of single-pool Kt/V values, resultant eKt/V values computed by different techniques can be expected to have relatively high correlations. A more stringent test of the rate equation is to analyze how well the difference between single-pool Kt/V and eKt/V, or the ΔKt/V, can be predicted from K/V and related parameters. Such an analysis is done in Tables 4 and 5 on a session basis, using all sessions (Table 4, $N = 295$), and using only non-deviant sessions (Table 5, $N = 262$).

When all sessions were analyzed, the univariate association (Pearson R value) between K/V and ΔKt/V was 0.40. The correlation coefficient increased to 0.56 when data from deviant

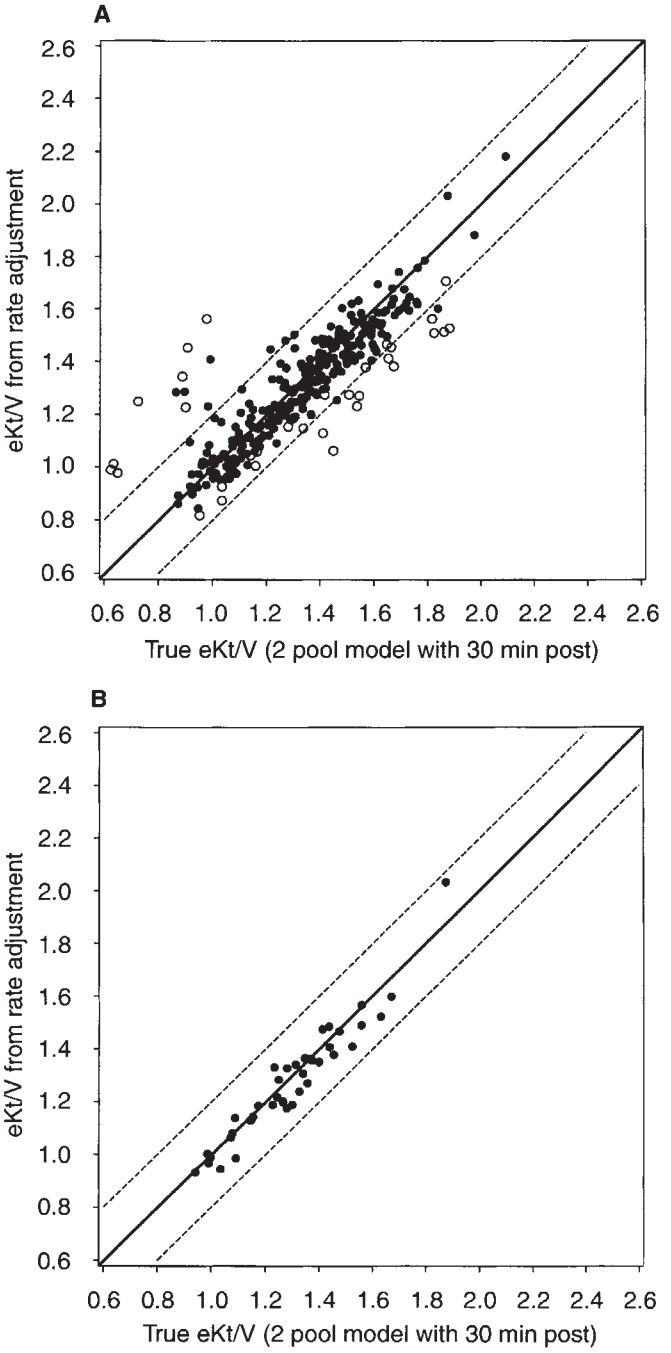

Fig. 1. Comparison of the true equilibrated eKt/V (based on the 2-pool model with the 30 min post-BUN) with results of the rate adjustment method. In Figures 1–4, the dashed lines indicate deviations of 0.2 Kt/V units. On the upper panel (*A*) of each figure, all sessions (baseline and follow-up, columns A–D in Table 1) are graphed. Deviant sessions (see text) are marked by open circles (○) but are not excluded from the analyses computing the correlation coefficients or mean/median differences. On the lower panel (*B*), only the baseline sessions on the usual dialysis prescription (column A in Table 1) are analyzed. Here the sessions are averaged after excluding deviant sessions to compute individual patient means, and the latter are graphed. (A) $N = 295$ session in 49 patients, $R_P = 0.854$, $R_S = 0.868$, $R_C = 0.843$, Med $\Delta = -0.04$, Med $|\Delta| = 0.064$, R_P (deviant sessions removed) = 0.919. (B) $N = 41$ patients (averages taken over 117 sessions, with deviant session excluded), $R_P = 0.960$, $R_S = 0.961$, $R_C = 0.954$, Med $\Delta = -0.02$, Med $|\Delta| = 0.037$.

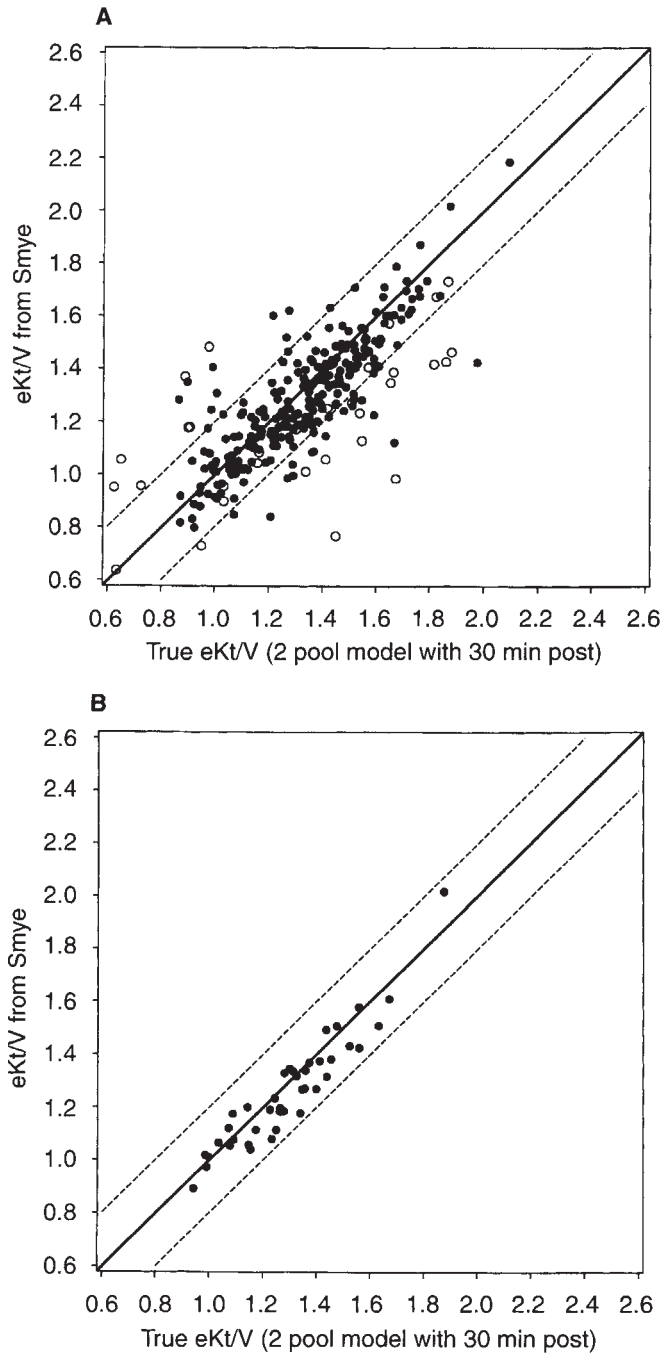

Fig. 2. Comparison of the true equilibrated eKt/V with results of the Smye method. (*A*) $N = 295$ session in 49 paticnts, $R_P = 0.779$, $R_S = 0.780$, $R_C = 0.761$, Med $\Delta = -0.06$, Med $|\Delta| = 0.087$, R_P [deviant sessions (○) removed] = 0.830. (*B*) $N = 41$ patients (averages taken over 117 sessions, with deviant session excluded), $R_P = 0.939$, $R_S = 0.931$, $R_C = 0.926$, Med $\Delta = -0.04$, Med $|\Delta| = 0.057$.

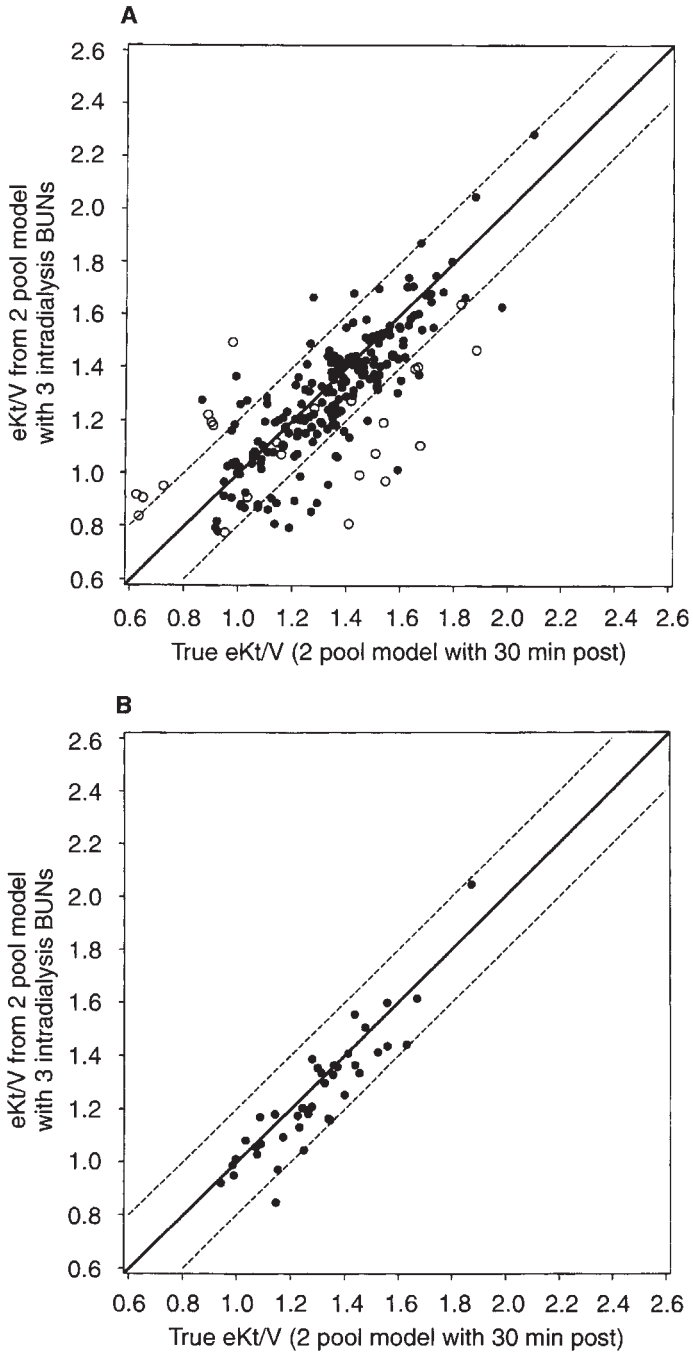

Fig. 3. Comparison of the true equilibrated eKt/V with results of the 2-pool model with 3 intradialysis BUNs. (*A*) $N = 229$ sessions in 49 patients, $R_P = 0.762$, $R_S = 0.761$, $R_C = 0.750$, Med $\Delta = -0.05$, Med $|\Delta| = 0.097$, R_P [deviant sessions (○) removed] = 0.819. (*B*) $N = 41$ patients (averages taken over 115 sessions, with deviant session excluded), $R_P = 0.907$, $R_S = 0.905$, $R_C = 0.882$, Med $\Delta = -0.04$, Med $|\Delta| = 0.056$.

sessions were excluded. The regression coefficients for K/V (0.60, 95% confidence limits 0.40 to 0.80 with all sessions included, and 0.67, 95% confidence limits 0.53 to 0.81 with deviant sessions omitted) were similar to the coefficient of 0.60 used by the rate equation. When K/V was first entered using a multiple regression model as a predictor of ΔKt/V, none of the remaining variables listed in Tables 4 and 5 (dialyzer clearance, time, ultrafiltration rate, urea distribution volume) showed any added predictive power for ΔKt/V.

Comparison of blood-side methods to the dialysate-derived eKt/V (BioStat method). A plot showing the correlation between eKt/V by the blood side standard (the 2-pool model with the 30 min

Table 2. Comparison of blood-sided measurements with the true equilibrated eKt/V: Analysis by individual dialysis session

Method	All modeled dialyses[a]					Sessions with deviant BUNs removed
	R_P	R_S	R_C	MedΔ	Med|Δ|	Rp
Rate equation[b]	0.85	0.87	0.84	−0.036	0.064	0.92
Smye[b]	0.78	0.78	0.76	−0.056	0.087	0.83
Two-pool model with 3 intradialysis BUNs[c]	0.76	0.76	0.75	−0.045	0.097	0.82

[a] With all modeled dialyses included, R_P, R_S, and R_C were significantly higher and med |Δ| significantly smaller ($P < 0.05$) for the rate equation than for the Smye method and for the 2-pool model with 3 intradialysis BUNs. Med Δ was significantly < 0 for each method, indicating each of these methods slightly underestimated the true eKt/V.

[b] All modeled dialyses (columns A–D in Table 1) including deviant sessions, $N = 295$ sessions in 49 patients, and excluding deviant sessions, $N = 262$ sessions in 48 patients.

[c] All modeled baseline dialyses (columns A–B in Table 1) including deviant sessions, $N = 229$ sessions in 49 patients, and excluding deviant sessions, $N = 203$ sessions in 48 patients. Number of sessions is lower for the 2-pool model with 3 intradialysis BUNs, as procurement of the additional intradialytic samples required was not done for sessions after randomization.

Table 3. Comparison of blood-side estimates with the true equilibrated eKt/V: Analysis by patient, after averaging eKt/Vs for 3–4 baseline dialyses at usual prescription (column A in Table 1)

	All modeled dialyses[a]					Sessions with deviant BUNs removed
	R_P	R_S	R_C	MedΔ	Med|Δ|	R_P
Rate equation[b]	0.89	0.88	0.88	−0.010	0.048	0.96
Smye[b]	0.92	0.91	0.90	−0.024	0.051	0.94
Two-pool model with 3 intradialysis BUNs[c]	0.87	0.89	0.85	−0.028	0.048	0.91

[a] With all modeled dialyses included, R_p, R_s, R_c, Med Δ and Med|Δ| did not differ significantly between the Rate equation, the Smye, and the 2-pool model with 3 intradialysis BUNs

[b] Including deviant sessions, $N = 131$ baseline dialyses in 41 patients; excluding deviant sessions, $N = 117$ dialyses in 41 patients

[c] Including deviant sessions, $N = 129$ baseline dialyses in 41 patients; excluding deviant sessions, $N = 115$ dialyses in 41 patients

Table 4. Univariate[a] associations between ΔKt/V = sp(Kt/V) − eKt/V and other parameters: All sessions

Parameter	Intercept (SE)	Slope (SE)	R	*P* value
K/V *liter/hr*	−0.05 (0.05)	+0.60 (0.10)	+0.40	< 0.0001
Td *hr*	+0.40 (0.07)	−0.053 (0.019)	−0.20	0.0006
Kd *liter/hr*	+0.04 (0.07)	+0.012 (0.004)	+0.17	0.003
V(sa) *liter*	+0.39 (0.07)	−0.005 (0.002)	−0.21	0.0003
Qf *liter/hr*	+0.21 (0.02)	+0.008 (0.023)	+0.03	0.60

N = All 295 sessions in 49 patients (columns A–D in Table 1).

[a] Univariate associations are presented because functional relationships among the other parameters preclude a multivariate model including all parameters. However, in separate regression models conducted with K/V and each of the other parameters considered one at a time, none of the remaining parameters were significant after including K/V.

Table 5. Univariate[a] associations between ΔKt/V = sp(Kt/V) − eKt/V and other parameters: Deviant sessions removed

Parameter	Intercept (SE)	Slope (SE)	R	*P* value
K/V *liter/hr*	−0.08 (0.03)	+0.67 (0.07)	+0.56	< 0.0001
Td *hr*	+0.37 (0.06)	−0.043 (0.015)	−0.30	< 0.0001
Kd *liter/hr*	+0.03 (0.05)	+0.013 (0.003)	+0.26	0.0001
V(sa) *liter*	+0.41 (0.06)	−0.005 (0.002)	−0.31	< 0.0001
Qf *liter/hr*	+0.20 (0.02)	+0.025 (0.020)	+0.06	0.33

Deviant BUN sessions removed (n = 262 sessions in 48 patients)

[a] Univariate associations are presented because functional relationships among the other parameters preclude a multivariate model including all parameters. However, in separate regression models conducted with K/V and each of the other parameters considered one at a time, none of the remaining parameters were significant after including K/V.

post-dialysis BUN) and eKt/V derived from the dialysate concentration profile is shown in Figure 4. Again, the upper graph shows all sessions (columns A-D in Table 1) with deviant blood BUN profiles identified as hollow circles and deviant dialysate profiles shown as crosses (deviant sessions not excluded from the analysis). The lower graph shows results from baseline modeling sessions at usual prescription only (column A in Table 1), with the results averaged by patient after excluding sessions with either deviant BUN or deviant dialysate urea nitrogen (DUN) profiles.

As shown by Table 6, the BioStat eKt/V was in closer agreement with the blood-side rate equation than with the Smye method or the 2-pool model with three intradialysis BUNs. As shown from a comparison of results in Table 6 and Table 2, agreement between the BioStat eKt/V and the blood-side standard based on the 2-pool model with the 30 min post-dialysis BUN (R_P of 0.68 or 0.76 with and without deviant sessions, respectively) was similar to the agreement of the rate equation or intradialytic methods with the 2-pool model with the 30 min post-dialysis (R_P values in the range of 0.76 to 0.85 with deviant sessions, and 0.82 to 0.92 with deviant sessions removed).

Error analysis: Rate method. Figure 5 shows results of urea modeling for every dialysis for each patient in a graphic format. The data are expressed as the difference between the true equilibrated eKt/V assessed using the 2-pool model with the 30 minute post-dialysis BUN and eKt/V predicted by the rate equation. Results for modeled dialyses during which the blood

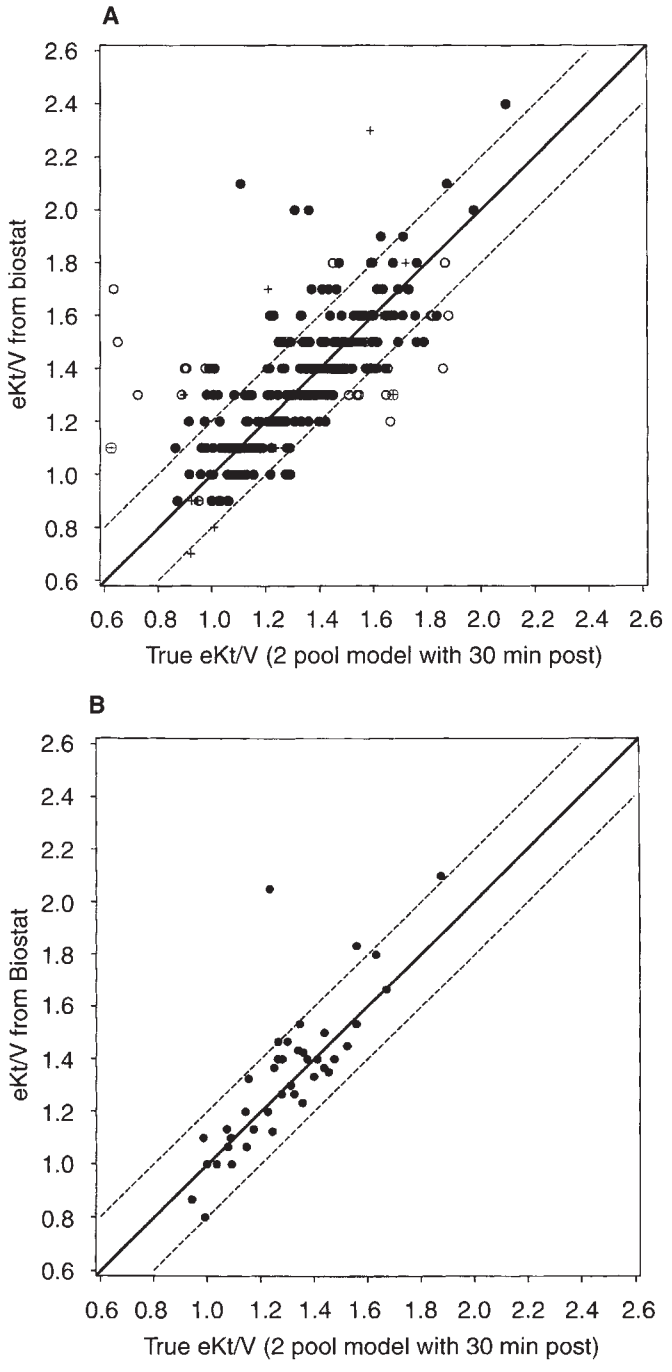

Fig. 4. Comparison of the true equilibrated eKt/V with results of the BioStat method. (*A*) N = 295 sessions in 49 patients, R_P = 0.682, R_S = 0.734, R_C = 0.679, Med Δ = +0.01, Med $|\Delta|$ = 0.078, r_P (deviant sessions removed) = 0.762. (*B*) N = 41 patients (averages taken over 101 sessions, with deviant session excluded), R_P = 0.813, R_S = 0.812, R_C = 0.762, Med Δ = +0.01, Med $|\Delta|$ = 0.076. Symbols are: (○) deviant BUN profile; (+) deviant DUN profile; (⊕) both.

BUN profiles were designated as deviant (fit errors) are shown as hollow circles. Figure 5 shows that modeled dialyses with fit errors were distinguishable from the usual values in the majority of patients.

DISCUSSION

The data suggest that post-dialysis urea rebound is relatively predictable in the study population that fulfilled enrollment criteria for the HEMO Pilot Study. Urea rebound could be predicted from curve fitting techniques that required one or more intradialysis BUN samples [17, 18], or from the single compartment Kt/V modified with a simple rate equation that was derived mechanistically from a model of urea kinetics based on regional blood flow [16, 23–25]. The excellent correlation of the true equilibrated eKt/V with that predicted by the rate equation suggests that the rise in BUN from the immediate post-dialysis period to 30 minutes post-dialysis is a function of the rate of dialysis (K/V). The rate equation is derived from a regional blood flow model, and although rebound (as ΔKt/V) is related to K/V, the slope term of the equation (the multiplier of the K/V term) was theorized to depend on the amount of blood flow going to those body organs in which urea content is high, but which normally receive only a small fraction of the cardiac output (for example, muscle). The slope coefficient of 0.60 was derived from the regional blood flow model based on an assumed cardiac index of 2.85 liter/min/m^2, a fractional flow to the "low flow, high urea volume" compartment of 15%, and an access blood flow of 800 ml/min [16, 26]. In a patient with either unusually good or unusually poor perfusion of the muscle (plus skin and bone) compartment, the regional blood flow model predicts that the 0.60 multiplier for the K/V term in the rate equation would be correspondingly lower or higher, reflecting decreased or increased urea sequestration in these organs. In fact, when a subset of patients with unusually high cardiac index is studied, rebound is smaller than that predicted by the rate equation [26]. The present data suggest that the 0.60 multiplier for the K/V term in the rate equation, as initially proposed by Schneditz and Daugirdas [24], is a reasonably good choice overall. The practical benefit is a simple linear equation (rate equation) that predicts the true equilibrated eKt/V fairly well. It remains possible that, for individual patients with unusual hemodynamic values (such as, unusually good or poor muscle perfusion), the rate equation will systematically and repeatedly under- or overestimate postdialysis urea rebound.

In designing a large multicenter trial to be carried out in 15 clinical centers, each with three or four dialysis clinics, the technique for assessing dialysis adequacy should be as simple as possible. The present study suggests that one need only measure the pre-dialysis and post-dialysis BUN and rely on expressions such as the rate equation to predict the effect of post-dialysis urea rebound on Kt/V.

Our results also suggest that use of one or more intradialysis BUN samples to estimate urea rebound [18] is a useful means of estimating the eKt/V. With regard to blood sampling during dialysis, the data suggest that a single sample obtained 70 minutes into dialysis affords as much information as multiple samples obtained throughout the dialysis. When estimating eKt/V for a single dialysis, the use of one or more intradialytic samples during dialysis to predict eKt/V was actually less accurate than using only the pre- and post-dialysis sample and the rate equation. A possible explanation for this result is that measurement error in the BUNs and/or physiologic fluctuations during dialysis may increase variability in methods, such as the Smye method or the 2-pool model with three intradialysis BUNs, which depend on the accuracy of session-specific estimates of the intercompartment mass transfer

Table 6. Comparison of blood-sided measurements with dialysis side eKt/V: Analysis by individual dialysis session

Method	All modeled dialyses[a]					Sessions with deviant DUNs and BUNs removed
	R_P	R_S	R_C	MedΔ	Med|Δ|	R_p
Two-pool model with 30 min post-BUN (blood side standard)[b]	0.68	0.73	0.68	+0.008	0.078	0.76
Rate equation[b]	0.77	0.78	0.74	−0.027	0.080	0.79
Smye[b]	0.64	0.67	0.61	−0.049	0.098	0.67
Two-pool model with 3 intradialysis BUNs[c]	0.59	0.60	0.57	−0.060	0.099	0.59

[a] With all modeled dialyses included, R_p and R_c were significantly higher ($P < 0.05$) for the agreement of the dialysate eKt/V with the rate equation than for the agreement of the dialysate eKt/V with the remaining three blood sided methods. R_s was also significantly higher and Med|Δ| significantly smaller for the agreement of the dialysate eKt/V with the rate equation than for the agreement of the dialysate eKt/V with the Smye or the 2-pool model with 3 intradialysis BUNs. Med Δ did not differ significantly from 0 for the true equilibrated eKt/V, indicating no systematic bias between the dialysate eKt/V and the blood side standard. Med Δ was significantly < 0 for the remaining blood side methods, indicating that these methods slightly underestimated the dialysate eKt/V.

[b] All modeled dialyses (columns A–D in Table 1) including deviant sessions; $N = 295$ sessions in 49 patients. Excluding deviant sessions; $N = 235$ sessions in 48 patients.

[c] All modeled baseline dialyses (columns A–B in Table 1) including deviant sessions; $N = 229$ sessions in 49 patients. Excluding deviant sessions; $N = 182$ sessions in 47 patients.

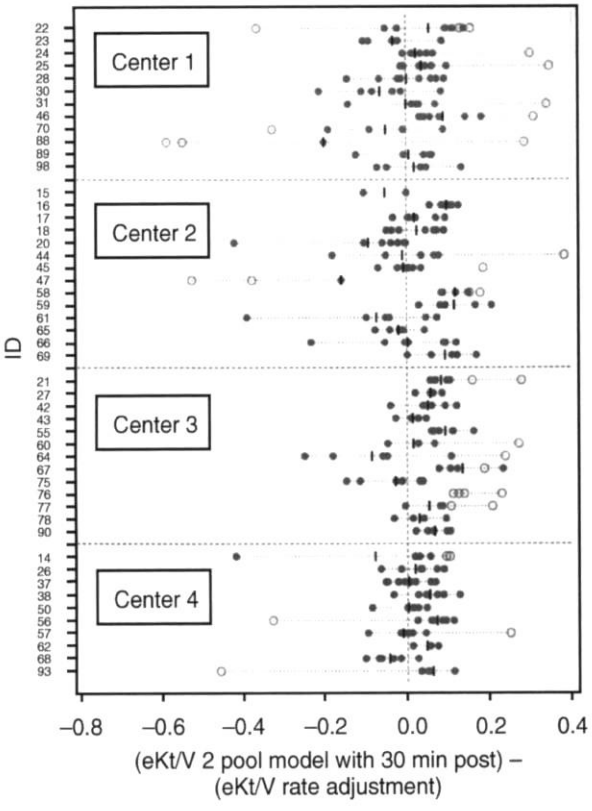

Fig. 5. Analysis by individual patient and by center of the difference between the true equilibrated eKt/V and eKt/V calculated from the simple rate equation. All sessions (baseline and follow-up, columns A–D in Table 1) are graphed. Deviant sessions (see text) are marked by open circles (○). The mean Kt/V difference for sessions with non-deviant BUN profiles are indicated by vertical bars. Sample size: 295 sessions in 49 patients.

coefficient Kc. By contrast, as described above, the rate equation assumes a constant level of solute disequilibrium that does not vary from session to session. The use of a fixed index of solute disequilibrium in the rate equation should produce less variable estimates of eKt/V for individual dialysis sessions, albeit possibly at the cost of bias in patients with unusual hemodynamic parameters. This explanation is supported by the observation that averaging eKt/Vs over three to four dialysis sessions improved the performance of the Smye method and the 2-pool model with three intradialysis BUNs to a level similar to that of the rate equation method (Table 3). That is, it appears that averaging results across several dialysis sessions smoothed out the variability induced by unstable estimates of Kc for the Smye method and the 2-pool model with three intradialysis BUNs.

One criticism of the design of the present studies is that blood was sampled only at 30 minutes after dialysis. Multicompartment models of urea kinetics predict that the degree to which rebound is complete at 30 minutes (usually 85 to 90%) depends on the intercompartment urea mass transfer coefficient, Kc, in addition to K/V. In theory, estimation of the equilibrated BUN from a single 30-minute post-dialysis BUN sample is problematic. This error could be reduced, although not eliminated, by waiting a full hour after dialysis to obtain a sample. Unfortunately, based on feedback from the clinical centers, it was deemed impractical to ask that the patients remain for a full hour after dialysis on multiple occasions. Hence a compromise time of 30 minutes post-dialysis was decided upon. Our analytical methods were designed to address the problem of incomplete rebound at 30 minutes. As discussed in the **Methods** section, there is a unique solution, or at most two solutions, for the classic 2-compartment model fitting values for the pre-dialysis BUN, the post-dialysis BUN, and the 30 minute post-dialysis BUN. When two solutions are found, one can be discarded because it requires a urea distribution volume that is far removed from the predicted anthropometric value. Thus, in a patient with a low value for Kc, the difference between the post-dialysis BUN and the 30 minute post-dialysis BUN will be larger (for similar values of K/V) than in a patient with a high value for Kc. Because the fractional completion of rebound at 30 minutes depends on Kc, both Kc and the 60 minute rebound value can be solved for iteratively, eliminating a bias that might be caused by an assumption that rebound is universally 85 to 90% complete 30 minutes after dialysis. An unproven assumption upon which the reliability of the

iterative curve fitting method depends is that the patient's urea kinetics strictly conforms to a two-compartment variable volume model. We have since obtained data in a subset of patients studied at 60 minute post-dialysis suggesting that the computational methods described here using a 30 minute post-dialysis BUN sample have an accuracy similar to that obtained using a 60 minute post-dialysis sample to predict the eKt/V (data not shown).

In this study a dialysate-based method of urea modeling was also assessed (BioStat, Baxter Healthcare, Inc.). There was little systematic difference in the mean equilibrated Kt/V values obtained from blood-side versus dialysate-side modeling, confirming reports by others that blood side modeling or dialysate modeling can be used to obtain equivalent equilibrated Kt/V values if the proper corrections are made for urea generation, urea removed during ultrafiltration, and post-dialysis urea rebound [27–29].

The correlations between the various blood-side methods in our study were higher than between the blood-sided methods and the dialysate-side measurement (BioStat). This finding is not unexpected, given that high correlations among the blood-sided methods of modeling are due partly to "mathematical coupling" among the blood-side methods due to common BUN inputs. For example, the Smye and the blood-side standard method based on the 2-pool model with the 30 minute post-BUN have the same input values for the pre- and post-BUN. Also, the blood-sided methods share a common Kd as input. A further bias is introduced in those analyses where "deviant" blood BUN profiles were removed. Although Figure 5 suggests that such sessions probably represented technical error in dialysate delivery or blood sampling, by screening "deviant" BUN profiles that are primarily a consequence of an aberrant relationship between the post-BUN and the 30 minute post-BUN values (negative or extremely large rebounds), one selects those sessions where the 30 minute post-BUN is strongly associated with the post-BUN. Where this screening was not performed, the correlations among the various blood side methods were reduced (compare the correlations computed with and without exclusion of the deviant sessions in Tables 2 and 3).

Because eKt/V could be measured several times on different occasions in the same patient, the data provided some insight regarding the stability and reproducibility of post-dialysis urea rebound from dialysis to dialysis. If one accepts the general principle of the rate equation, then ΔKt/V (the difference between single-pool Kt/V and eKt/V) is mainly determined by the rate of dialysis, or K/V. Figure 5 gives some measure of the residual variability within and among patients in ΔKt/V once the K/V effect has been controlled for. In Figure 5, we subtract estimated ΔKt/V based on K/V from the actual ΔKt/V. It can be seen that on average, post-dialysis urea rebound was predictable for most patients, although it was not uncommon to have one or more sessions that were deviant (hollow circles in Figure 5), the BUN values of which could not be fit with the standard 2-pool urea model.

Based on the results of this Pilot Study, a decision was made to calculate the dose of each dialysis during the Full Scale HEMO Study from a single-pool Kt/V corrected to the equilibrated Kt/V value using the rate equation, and to perform periodic validations of the rate equation assumptions using the Smye technique, occasional 30 minute post-dialysis samplings and, in a subset of patients, 60 minute post-dialysis samplings for BUN. A dialysate method using multiple dialysate urea samplings (BioStat) is also being used to validate the rate equation method in a subset of patients.

In summary, our results suggest that, in a dialysis patient population selected for ability to achieve an equilibrated Kt/V of about 1.45 in less than a 4.5 hour period, use of the pre- and post-dialysis samples and a kinetically-derived rate equation gives reasonably good prediction of equilibrated Kt/V. Addition of one or more intradialytic samples does not appear to increase accuracy of predicting the equilibrated Kt/V in the majority of patients. A method based on dialysate urea analysis and curve-fitting yields results for equilibrated Kt/V that are similar to those obtained using exclusively blood-based methods of kinetic modeling.

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Reprint requests to Gerald J. Beck, Ph.D., HEMO Study Data Coordinating Center, Department of Biostatistics and Epidemiology, P88, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44195, USA.

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