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DIALYSIS – TRANSPLANTATION

Imprecision of the hemodialysis dose when measured directly from urea removal

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Imprecision of the hemodialysis dose when measured directly from urea removal.

Background. The postdialysis blood urea nitrogen (BUN; C_t) is a pivotal parameter for assessing hemodialysis adequacy by conventional blood-side methods, but C_t is relatively unstable because of hemodialysis-induced disequilibrium. The uncertainty associated with this method is potentially reduced or eliminated by measuring urea removed on the dialysate side, a more direct approach that can determine adequacy from the fraction of urea removed and by substituting an estimate of the equilibrated postdialysis BUN (C_{eq}) for C_t. For a patient with a known urea volume (V), C_{eq}, the equilibrated Kt/V (eKt/V), and the solute removal index (SRI) can be calculated from the predialysis BUN (C_0), total urea nitrogen removed (A), and V from simple mass balance calculations (dialysate/volume method). However, a theoretical error analysis showed that relatively small errors in A, C_0, or V are magnified when SRI or eKt/V is calculated using this method, especially at higher eKt/V values (for example, if eKt/V = 1.4 per dialysis, a 7% dialysate collection error causes a 20% error in eKt/V).

Methods. During three to four baseline dialyses in each of 39 patients enrolled in the pilot phase of the HEMO Study, "A" was measured using an instrument that sampled dialysate frequently (Biostat®), and V was calculated from A, C_0, and C_{eq} (median CV for V = 5.6%). The mean V was then applied to the dialysate/volume method to estimate eKt/V and SRI during two to five subsequent dialyses per patient (comparison dialyses). The accuracy and precision of these estimates were assessed by comparing them with eKt/V and SRI derived from a direct measurement of C_{eq} drawn 30 minutes after dialysis (reference method), from mathematical curve-fitting of sequential dialysate urea concentrations (dialysate curve-fit method), and from another blood-side method that estimates eKt/V from single pool Kt/V and the fractional rate of solute removal (rate method): $eKt/V = spKt/V - 0.6 \cdot K/V + 0.03$.

Results. During 128 comparison dialyses, median absolute errors for calculated eKt/V compared with the reference method were 0.169, 0.061, and 0.071 for the dialysate/volume method, the rate method, and the dialysate curve-fitting method, respectively. The corresponding correlation coefficients were 0.47, 0.88, and 0.81. For SRI, median absolute errors were 0.044, 0.018, and 0.027, and the correlation coefficients were 0.54, 0.85, and 0.74 for the three methods.

Conclusions. The precision of eKt/V and SRI measurements was significantly lower for the dialysate/volume method compared with the blood-side methods. Inclusion of the dialysate curve analysis provided by the Biostat® restored precision to the dialysate method to a level comparable to that of the blood-side methods. New techniques employing dialysate urea analysis should include a concentration profile to avoid these inherent methodological errors and assure the accuracy of eKt/V and SRI.

The most commonly used methods for quantitating hemodialysis are based on measurement of the dialysis-induced fall in serum urea concentration (BUN) [1–5]. Because the fall in BUN is an indirect measure of the primary effect of dialysis, the removal of solute, an alternative, more direct measurement of urea loss on the dialysate side, has been proposed [6–9]. Dialysate-based methods may also be used to measure the dialyzer urea clearance, independent of blood flow measurements, and the patient's true urea distribution volume (V). The latter coincides with total body water, a relatively constant physiologic parameter. Development of an instrument

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(Biostat 1000®; Baxter Healthcare Corporation, McGaw Park, IL, USA) to facilitate on-line measurement of relatively low dialysate urea concentrations sparked new interest is this approach [10, 11]. The new dialysate methodology allows more accurate measurement of urea removal by eliminating problems with bacterial contamination and other sources of error that confounded previous dialysate methods.

In current practice, hemodialysis dosage is often expressed as the urea reduction ratio (URR) or as Kt/V derived from single pool mathematical modeling of urea mass balance (spKt/V). The latter is a measure of dialyzer clearance expressed per dialysis (instead of per minute) and expressed as a fraction of the urea distribution volume (instead of body surface area). On the blood side, both URR and spKt/V are determined primarily from the fractional reduction in BUN during dialysis, but spKt/V also includes the effects of urea generation and ultrafiltration [12]. Dependence on the postdialysis BUN measurement is often cited as a weakness of these current blood-side techniques [11, 13]. The postdialysis BUN is difficult to measure because precautions must be taken to avoid distortion caused by vascular access recirculation and by dilution of the sample with intravenous fluids (saline, blood, and other solutions) often given near the end of the treatment. In addition, cardiopulmonary and venovenous recirculation during dialysis induce a urea concentration disequilibrium between the blood entering the dialyzer and the patient. This urea gradient quickly reverses beginning approximately 10 to 20 seconds after slowing or stopping dialysis and is accompanied by a rapid rise in the BUN [14]. The instability of the postdialysis BUN caused by all of these conditions necessitates precise timing of the sampling, within a short time window (measured in seconds), to avoid errors in the modeled parameters [15, 16].

Even when these sources of error are eliminated, blood-side methods routinely overestimate the effective dialysis dose because the BUN continues to rebound, although more slowly, for 20 to 60 minutes following dialysis. Rebound is caused by re-equilibration of multiple urea concentration gradients that develop within the patient during dialysis when solute removal is relatively rapid [17–19]. Thus, accurate blood-side assessment of the effective dialysis dose requires an estimation of the postdialysis BUN after urea concentrations have fully equilibrated within the patient. This can be accomplished either by directly measuring the BUN at least 30 minutes after dialysis, at substantial inconvenience to the patient and staff, or by predicting the equilibrated postrebound BUN assuming a specific mathematical model of rebound [20–22]. When the equilibrated postdialysis BUN is used in place of the immediate postdialysis BUN to calculate spKt/V and URR, the analogous results are the equilibrated Kt/V (eKt/V) and the solute removal index (SRI), respectively. The SRI is an estimate of the fraction of urea removed during dialysis, which, unlike URR, also takes into account urea generation and ultrafiltration [23].

In principle, if urea can be measured in the dialysate, the calculation of the dialysis dose is more straightforward, is constrained by fewer assumptions than blood-based methods, and does not require routine measurement of the postdialysis BUN. This direct quantitation approach compares the amount of urea removed during dialysis with the amount of urea present in the patient at the start of dialysis. In the absence of urea generation and fluid volume changes:

$$V = A/(C_0 - C_{eq}) \quad \text{(Eq.1)}$$

$$C_{eq} = C_0 - A/V \quad \text{(Eq.2)}$$

Because it was envisioned as a possible future standard for quantitating hemodialysis, this approach was included in the pilot phase of the HEMO Study, a prospective multicenter clinical trial of the effects of dialysis dose and membrane flux on survival [24]. In the pilot study, each patient's V was first estimated from the amount of urea removed in the dialysate and the net fall in BUN (to equilibrium) during each of three baseline treatments. For subsequent modeled dialyses, the patient's predialysis urea content was calculated as the product of this estimate of V and the predialysis BUN. The SRI and eKt/V for these dialyses were then calculated from the patient's estimated predialysis urea content and the measured loss of urea in the dialysate. This technique is subsequently referred to as the "dialysate/volume method."

The HEMO pilot study provided an opportunity to assess the performance of several blood-side or dialysate-side methods to estimate eKt/V and SRI. To provide a reference for comparison, the pilot study protocol included a blood sample obtained 30 minutes after termination of dialysis. The SRI and eKt/V calculated using this value were used as reference standards to which results of the dialysate/volume method and several alternative methods that do not require delayed postdialysis sampling were compared. The objective of this report is to evaluate the performance of the dialysate/volume method in comparison with these alternative blood-side and dialysate-side methods.

Comparisons of the agreement of kinetic parameters estimated by the different methods with corresponding parameters calculated from the 30-minute postdialysis BUN are not entirely conclusive because of error coupling among the blood-side estimates that use common BUN measurements. When analyzing errors, one must consider the possibility that the level of agreement observed among the blood-side estimates could be en-

hanced by the commonality of BUN measurements that enter into each estimate. To avoid this pitfall, we included analyses comparing the dialysate/volume and blood-based techniques to a recently developed dialysate technique that is based on mathematical curve fitting of dialysate urea concentrations measured throughout dialysis [10]. Dialysate urea concentrations were measured on-line in near real time by an analyzer that was different from the analyzer used to measure BUN, thus reducing the likelihood that errors would be coupled to errors in blood-side measurements.

We also conducted a statistical error analysis to compare the within-patient variability of eKt/V and SRI, calculated by the dialysate/volume method, with the within-patient variability of eKt/V and SRI calculated by the blood-side methods. This analysis compared the effects of different sources of measurement error among the methods without the confounding effects of error coupling.

METHODS

Study design

Data were collected during the pilot phase of the HEMO Study, a large multicenter interventional study of the effect of hemodialysis dose and membrane permeability on patient morbidity and mortality over a prolonged time [24]. For the pilot phase that was designed to examine the feasibility of conducting the full-scale study, patients maintained for at least six months on hemodialysis three times a week were selected from four clinical centers: Beth Israel Medical Center, New York, New York; Harbor-UCLA Medical Center, Los Angeles, California; New England Medical Center/St. Elizabeth's Hospital, Boston, Massachusetts; and Vanderbilt University Medical Center, Nashville, Tennessee, USA. Qualified patients who consented to enroll were studied during three phases while undergoing hemodialysis three times weekly.

Phase I. During a baseline observational period that lasted approximately three weeks, potential study participants were treated with their usual dialysis prescription. Urea kinetics were modeled, and dosage parameters were calculated from BUN values obtained during and 30 minutes following three to four dialyses in each patient.

Phase II. During the subsequent two weeks, patients were treated with a dialysis prescription that targeted eKt/V at 1.40 per dialysis. Urea kinetics were modeled during two to four dialyses in this phase.

Phase III. Patients who successfully achieved the minimum target eKt/V during phase II and who satisfied other study eligibility criteria were randomized to a target eKt/V of 1.00 or 1.40 per dialysis three times weekly. Each patient had two modeled dialyses during the subsequent two weeks. This report does not separate patients based on their randomized target eKt/V, but instead examines the aggregate of delivered eKt/V values measured by the four methods described later here. Analyses of the effects of randomization on dialysis dose are described elsewhere [25].

Procedures

For all modeled dialyses, blood samples for BUN determination were drawn before starting dialysis (C_0), after reducing blood flow to 100 to 120 ml/min for 10 seconds after terminating dialysis (C_t), and 30 minutes after dialysis (C_{30}). All BUN concentrations were measured at a central biochemistry laboratory (Spectra Laboratories, Inc., Fremont, CA, USA). For external quality control, 52 sets of blood samples were obtained predialysis (C_0), after 70 minutes of dialysis, and at the end of dialysis (C_t). Each of these samples was split into two aliquots by the clinical center and was shipped on different days to the central biochemistry laboratory for blinded analysis.

An instrument designed to measure dialysate urea nitrogen concentrations at frequent intervals (Biostat 1000®) was attached to the effluent dialysate line during all studied dialyses [10, 11]. Dialysate urea concentration was measured at five-minute intervals during the first 30 minutes of dialysis and at 10-minute intervals thereafter. Total dialysate urea nitrogen (A) was computed as the product of the dialysate flow, which was assumed constant, and the integrated dialysate concentration profile. An estimate of the predialysis BUN was obtained from a dialysate sample that was equilibrated with the blood at the start of dialysis.

Measuring the amount of urea in the dialysate may also incur errors, but the errors are easier to avoid. Potential problems with collecting, mixing, and storing large amounts of dialysate; loss of dialysate urea from bacterial contamination; and the problem with measuring typically low dialysate urea concentrations have been circumvented by the Biostat 1000®, an instrument that samples dialysate and measures urea concentrations on-line [11, 26]. Urea concentrations in the dialysate are based on a coupled urease/conductivity method optimized for the low urea concentrations found in dialysate, especially toward the end of the dialysis treatment [10]. Frequent measurements of dialysate urea concentration by this instrument, especially early in dialysis when a proportionately larger amount of urea is removed and concentrations are more critical, increase the precision and accuracy of total urea removal. The instrument also includes a program for analyzing the dialysate concentration/time curve used for the curve-fitting method described earlier here. For the dialysate/volume method used in this study, the curve fitting and other features of the Biostat® were ignored, and the instrument was

used solely to calculate the amount of urea removed during each dialysis from integration of the periodic 5- and 10-minute dialysate sample concentrations and measured dialysate flow rates.

Patients

As reported previously, complete kinetic modeling data were obtained from 295 dialyses in 49 pilot study participants [25]. In this report, analyses were restricted to 39 of these patients who had complete data for at least three phase I and at least one phase II or phase III modeled dialyses. Although 8 of these 39 patients had four phase I modeled dialyses, analyses were restricted to the first three phase I modeled dialyses for consistency. We also excluded one modeled dialysis in phase II for which the dialysate/volume method produced a negative estimate for the equilibrated postdialysis BUN. With these restrictions, this report is based on 117 modeled dialyses in 39 patients during phase I, 72 modeled dialyses in the same 39 patients during phase II, and 56 modeled dialyses in 30 of these patients who were randomized in phase III. The median age of the 39 patients considered in the report was 61.8 (range 29.0 to 75.5) years. Twenty-four were males, 21 were African American, and 20 were diabetic.

Calculations of eKt/V and SRI

Two blood-side and two dialysate-side methods were compared. For each of the blood-side methods and for the dialysate/volume method, we first estimated the equilibrated postdialysis BUN concentration (C_{eq}). Given C_{eq} for a particular method, we then computed the corresponding eKt/V from C_0, C_{eq}, and an estimate of urea volume using a single compartment variable volume model of urea kinetics [1, 3, 27]. For each of the four methods, the SRI [23] was computed from C_0, C_{eq}, the change in patient weight during dialysis, and an estimate of the equilibrated urea generation rate. These calculations are described in more detail later here.

Blood-side methods

The reference method. A two-compartment, variable-volume, diffusion model of hemodialysis urea kinetics was first fit to C_0, the adjusted C_t, and the 30-minute postdialysis BUN (C_{30}) using the theoretical dialyzer clearance (K_d). This model provided estimates of the intercompartment transfer coefficient (K_c) and the total urea volume (V), which were then used to estimate the fully equilibrated BUN (C_{eq}) after correction for postdialysis urea generation. Before applying the model, a slight upward adjustment was made in the measured postdialysis BUN (C_t) to account for cardiopulmonary recirculation. The adjusted C_t was defined as C_t/F_{cp}; the adjustment factor (F_{cp}) was calculated assuming average values for cardiac output (CO) and access blood flow (Q_{ac}) [14]:

$$F_{cp} = 1/[1 + K_{ac}/(CO - Q_{ac})] \qquad \text{(Eq.3)}$$

where K_{ac} is the access clearance. Q_{ac} was assumed to be 800 ml/min, and CO was estimated assuming a mean cardiac index of 3.0 per m^2 body surface area.

The reference method depends heavily on C_{30}, but it is important to add that C_{30} is not simply used as a substitute for C_{eq}. The latter is determined from a formal two-compartment model of urea kinetics applied individually to each patient.

A value for eKt/V was then computed by applying a single-compartment, variable-volume model of hemodialysis urea kinetics to C_0, C_{eq}, the intradialysis weight loss, and the estimated total V [3, 28].

The solute removal index was computed as follows [23]:

$$SRI = \frac{C_0[V + Qf \cdot T_d] - V \cdot C_{eq} + G \cdot T_d}{C_0[V + Qf \cdot T_d]} \qquad \text{(Eq.4)}$$

where Qf is the rate of weight lost during dialysis, and T_d is the treatment time. V is the patient's total V postdialysis, and G is an estimate of the urea generation rate; both were determined from the two-compartment model described earlier here.

The rate adjustment method. This method assumes that the rebound in BUN after completion of dialysis is related to the fractional rate of urea removal (K_d/V) during dialysis [22]:

$$eKt/V = spKt/V - 0.6 \cdot K_d/V + 0.03 \quad (K_d \text{ is expressed as ml/hr}) \qquad \text{(Eq.5)}$$

Here, spKt/V is the estimate of Kt/V obtained from single-compartment urea kinetic modeling using C_0 and the measured postdialysis C_t [3, 27]. To calculate SRI by this method, we first obtained an estimate of the whole body clearance (K_{wb}):

$$K_{wb} = eKt/V \cdot V/T_d \qquad \text{(Eq.6)}$$

K_{wb} and V were used to calculate C_{eq} from the single-compartment, variable-volume model. SRI was then calculated using equation 4.

Dialysate-side methods

The dialysate curve-fit method. The profile of dialysate concentration versus elapsed time obtained from the Biostat® was fitted to a double exponential curve by a previously described technique [10, 11]. The parameters that described these curves were used to compute the

Table 1. Patient characteristics (mean ± SD)

Factor	Phase I (original prescription)	Phase II (pre-randomization, target eKt/V = 1.4/dialysis)	Phase III (post-randomization target eKt/V = 1.0 or 1.4/dialysis)
Number of patients	39	39	30
Postdialysis weight *kg*	70.5 ± 15.6	70.2 ± 15.3	70.7 ± 13.5
Watson V *Liter*	36.6 ± 7.1	36.6 ± 7.1	36.8 ± 6.6
|Change| in Watson V from phase I *liter*	—	−0.1 ± 0.4	−0.1 ± 0.4
Treatment time *min*	208 ± 27	220 ± 31	219 ± 34
Dialyzer clearance *ml/min*	247 ± 29	275 ± 29	234 ± 33
eKt/V	1.27 ± 0.20	1.41 ± 0.24	1.31 ± 0.24
SRI	0.72 ± 0.06	0.76 ± 0.08	0.73 ± 0.06

patient's effective or whole-body urea clearance (K_{wb}), the patient's total urea V, the eKt/V, and SRI. In 29 of the modeled dialyses considered in this report, a predialysis equilibrated dialysate sample, which is normally used by the Biostat to estimate the predialysis BUN, was not obtained. In its place, we used the measured predialysis BUN. The estimated predialysis BUN is not used by the Biostat for determining either eKt/V or the total urea removed, but does have a small effect on the Biostat estimate of SRI.

The dialysate/volume method. The dialysate/volume method comprised two stages. In the first stage, which included the three modeled dialyses during phase I of the baseline period, the patient's postdialysis V was estimated at each modeled dialysis by the following:

$$V = [A - T_d \cdot (G + Qf \cdot C_0)]/(C_0 - C_{eq}) \quad \text{(Eq.7)}$$

where C_0 is the predialysis BUN, C_{eq} is the equilibrated BUN from the observed 30-minute rebound method (see **The Reference Method** section), G is the equilibrated urea nitrogen generation rate, T_d is the treatment time, and Qf is the ultrafiltration rate. The estimates of V from the three modeled dialyses in phase I were averaged to obtain a mean V (V_m) for each patient. In subsequent modeled dialyses during phases II and III of the pilot study, the amount of urea removed and the predialysis BUN from the current modeled dialysis were used along with the previously obtained V_m to estimate C_{eq} based on the following rearrangement of Equation 7:

$$C_{eq} = C_0 - [A - T_d \cdot (G + Qf \cdot C_0)]/V_m \quad \text{(Eq.8)}$$

Given C_{eq}, eKt/V and SRI were computed as described earlier here for the other methods.

To detect possible confounding effects of longitudinal changes in weight, the anthropometric volume was also calculated for each modeled dialysis (Table 1) [29].

Statistical methods

Assessment of the agreement between estimates of SRI and eKt/V. We assessed the performance of the dialysate/volume method by comparing estimates of eKt/V and SRI calculated by the dialysate/volume method to corresponding estimates obtained from the reference method (30-minute rebound) and the dialysate curve-fit method in each patient during the 128 modeled dialyses of phases II and III. Comparisons included the median Δ to assess systematic bias between methods, the Pearson correlation (Pearson R) to assess linear association, the Spearman correlation (Spearman R) to assess general monotonic association, and the median absolute Δ and concordance correlation coefficient [30] to assess the agreement between methods. The concordance correlation approaches a value of one if there is perfect agreement between methods.

The level of agreement within patients for the dialysate/volume method was compared with the agreement among the blood and dialysate methods. The bootstrap method [31] with 1,200 independent bootstrap samples was used to determine approximate *P* values for these comparisons. To account for multiple dialysis modelings for each patient, the bootstrap resampling was done on a patient basis rather than an individual dialysis treatment basis.

Error analysis

A statistical error analysis is used to describe the effect of errors in measurements of BUN and total urea removal on the calculated values of SRI and eKt/V obtained by the different methods. To simplify the presentation, we ignored ultrafiltration and intradialysis urea generation in the error analysis. Then SRI by the dialysate/volume method reduces to:

$$SRI_{Vol} = \frac{A}{C_0 \cdot V_m} = 1 - \left(\frac{(C_0 - A/V_m}{C_0}\right) \quad \text{(Eq.9)}$$

whereas SRI from a blood-based method is:

$$SRI_{blood} = 1 - \left(\frac{C_{eq(blood)}}{C_0}\right) \quad \text{(Eq.10)}$$

where $C_{eq(blood)}$ is the estimated equilibrated BUN for the blood-based method under consideration. Under this

simplification, the equilibrated Kt/V values associated with the dialysate/volume and blood-based methods are $-\ln(1 - SRI_{Vol})$ and $-\ln(1 - SRI_{blood})$, respectively.

Errors in SRI

As shown in **Appendix B**, the coefficient of variation (CV denoted by τ) of SRI that is due to measurement error in the dialysate/volume method is approximated by the following:

$$\tau(SRI_{Vol}) \cong \sqrt{\tau^2\,(A) + \tau^2(C_0) + \tau^2\,(V)/N} \qquad \text{(Eq.11)}$$

where $\tau^2(A)$ and $\tau^2(C_0)$ are the squared CVs of the estimates of total urea removal and the predialysis BUN for the current treatment session, $\tau^2(V)$ is the squared CV of the estimates of V from equation 7 during the prior modeled dialyses, and N is the number of prior dialyses used in computing the average volume (V_m). In this study, $N = 3$ for each patient.

The CV of SRI from blood-side methods is approximated by the following:

$$\tau(SRI_{blood}) \cong \frac{C_{eq(blood)}}{C_0 - C_{eq(blood)}} \times \sqrt{\tau^2(C_0) + \tau^2(C_{eq(blood)}) - 2\rho \cdot \tau(C_0) \cdot \tau(C_{eq(blood)})} \qquad \text{(Eq.12)}$$

where $C_{eq(blood)}$ is the estimated equilibrated BUN from the blood-side method and ρ denotes the correlation coefficient of the errors in C_0 and $C_{eq(blood)}$.

Errors in eKt/V

We show in **Appendix B** that the CV of measured eKt/V for a patient dialyzed with a given SRI and eKt/V is related to the CV for the measured SRI by the approximation:

$$\tau(eKt/V_{Vol}) \cong \frac{SRI}{(eKt/V) \cdot (1 - SRI)} \cdot \tau(SRI) \qquad \text{(Eq.13)}$$

Equation 13 follows from the approximate logarithmic relationship between eKt/V and SRI and holds regardless of what method is used to estimate SRI and eKt/V. Equations A-1 and A-2 of **Appendix A** give explicit expressions for the CV of eKt/V for the dialysate/volume method. Equation 13 shows that the CVs for eKt/V and SRI calculated by a particular method at a particular dialysis dose are directly related by the factor $SRI/[eKt/V \cdot (1 - SRI)]$. Hence, a method that produces a more (or less) reliable estimate of SRI will also tend to produce a more (or less) reliable estimate of eKt/V. To simplify the presentation, comparisons of the precision of the different methods are therefore given in terms of SRI only.

Estimation of coefficients of variation

The coefficients of variation in the statistical error analysis were estimated using the bias-corrected maximum likelihood method described by Connett and Lee [32]. The CVs for C_0 and C_t were estimated by applying this method to the 52 quality control specimens submitted to the clinical laboratory as split samples (see **Procedures** section). The CV of V was similarly estimated from the values of V determined by equation 7 for the three modeled dialyses during phase I.

RESULTS

Patient characteristics

Dialysis outcome data for the 39 patients included in this study are summarized in Table 1, including the initial phase I dialyses while the patients remained on their original prescriptions, phase II (prescribed eKt/V = 1.4), and phase III following randomization. Dialyzer clearance was measured on the blood side. During phase I, the coefficients of variation of V determined from equation 7 ranged from 1.1% to 34.2%, with a median of 5.6%, and 25th and 75th percentiles of 3.2% and 10.9%, respectively. The bias-corrected maximum likelihood estimate of the parameter $\tau(V)$ considered in the statistical error analyses was 11.0%. The lower value of the median CV compared with the bias-corrected estimate is expected, as the median CV has a substantial negative bias as an estimate of $\tau(V)$ when the number of observations per patient is small, as is the case here ($N = 3$ per patient).

Comparison of agreement among estimates of SRI and eKt/V

The agreement among the estimates of SRI from the three blood-side and dialysate curve-fit methods is summarized in the top three panels of Figure 1 and in the top three rows of Table 2. The agreement of the SRI from the dialysate/volume method with the SRIs from these three methods is summarized in the bottom three panels of Figure 1 and in the bottom three rows of Table 2. Each of the four measures, median $|\Delta|$, Pearson R, Spearman R, and the concordance correlation, indicate a poorer agreement between the dialysate/volume method and each of the three blood-side and dialysate curve-fit methods than among the three blood-side and dialysate curve-fit methods themselves.

Figure 2 and Table 3 show a similar analysis and the level of agreement among each of the methods for estimating eKt/V. Here too, the median $|\Delta|$, Pearson R, Spearman R, and the concordance correlation indicate a poorer agreement of the dialysate/volume method with

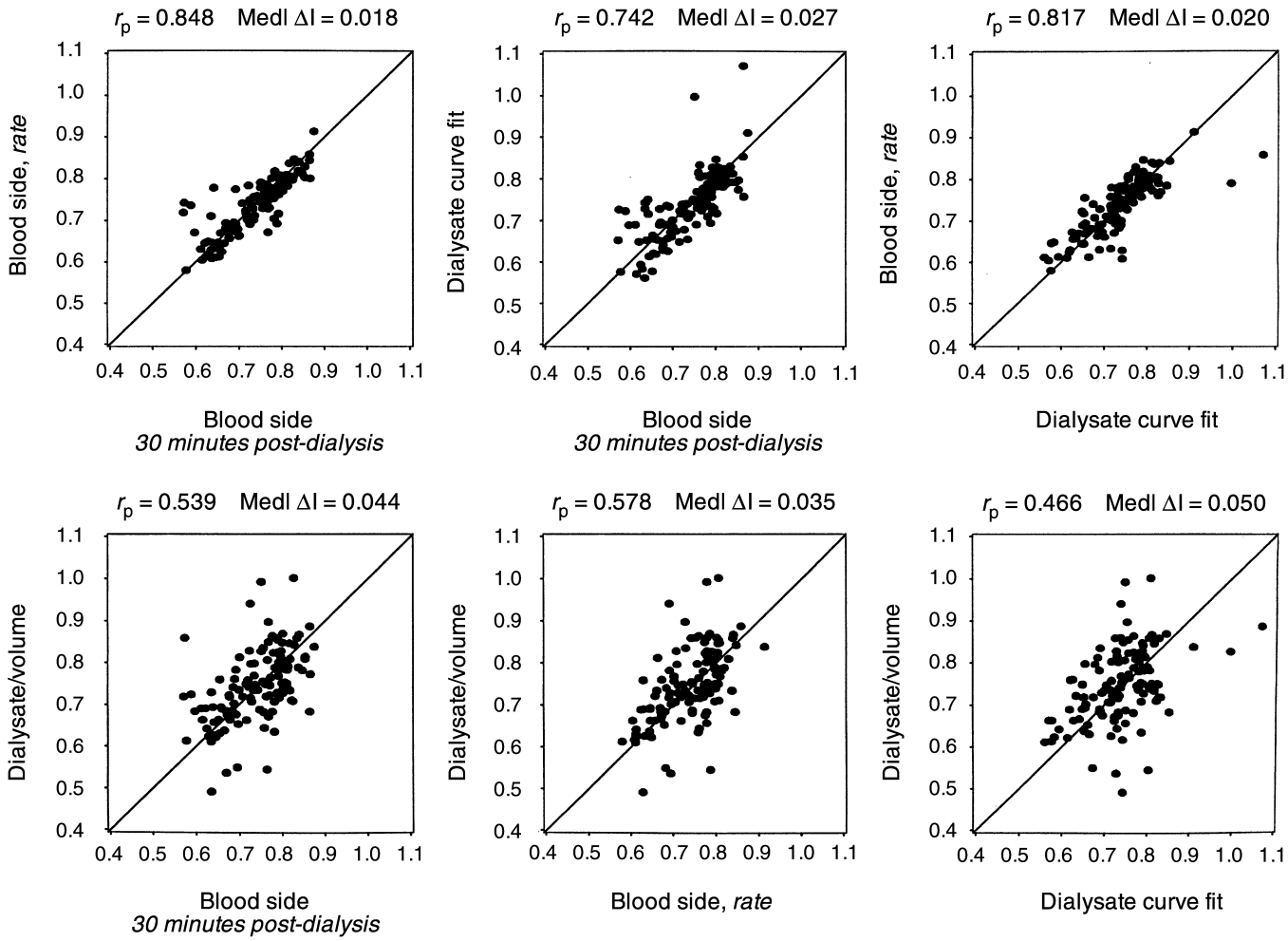

Fig. 1. Each plot shows the solute removal index (SRI) from 128 modeled dialyses in phases II and III of the HEMO pilot study. Methods for determining SRI are shown on the x-axis and y-axis of each plot. "Blood Side, 30 Min Post" is the reference method based on the 30-minute postdialysis BUN. "Blood Side Rate" is the method derived from the spKt/V and the rate equation. "Dialysate curve fit" is the method based on mathematical fitting of the dialysate concentrations. The three bottom panels show the correlation of the dialysate/volume method with each of these three methods (Table 2). R_p is the Pearson correlation coefficient. Med |Δ| is the median absolute value of the deviation.

Table 2. Comparisons of the solute removal index (SRI) derived from different methods

Methods compared[a]	Median Δ	Median |Δ|	Spearman R	Pearson R	Concordance R
Blood-side rate equation vs. blood-side reference	−0.009	0.018	0.87	0.85	0.84
Dialysate curve fit vs. blood-side reference	−0.011	0.027	0.81	0.74	0.74
Dialysate curve fit vs. blood-side rate equation	−0.003	0.020	0.86	0.82	0.81
Dialysate/volume vs. blood-side reference	+0.002	0.044	0.58	0.54	0.53
Dialysate/volume vs. blood-side rate equation	+0.008	0.035	0.60	0.58	0.56
Dialysate/volume vs. dialysate curve fit	+0.015	0.050	0.50	0.47	0.46

Data were obtained from 128 Phase II and Phase III modeled dialyses.

[a] For each of the correlation measures, Spearman R, Pearson R, and Concordance R, the agreement among the two blood-side methods and the dialysate-side curve fit method (top three rows) was significantly better ($P < 0.05$) than the agreement of the dialysate/volume method with each of the other three methods (bottom three rows). For median |Δ|, the agreement of the blood-side rate equation with both the blood-side reference (first row) and the dialysate curve fit (third row) were significantly better ($P < 0.05$) than the agreement of the dialysate/volume method with each of the other three methods (bottom three rows). The agreement of median |Δ| between the dialysate curve fit and blood side reference (second row) was also significantly better than the agreement of the dialysate/volume with both the dialysate curve fit and the blood-side rate equation ($P < 0.05$), but was not significantly better than the agreement of the dialysate/volume method with the blood-side standard ($P = 0.19$).

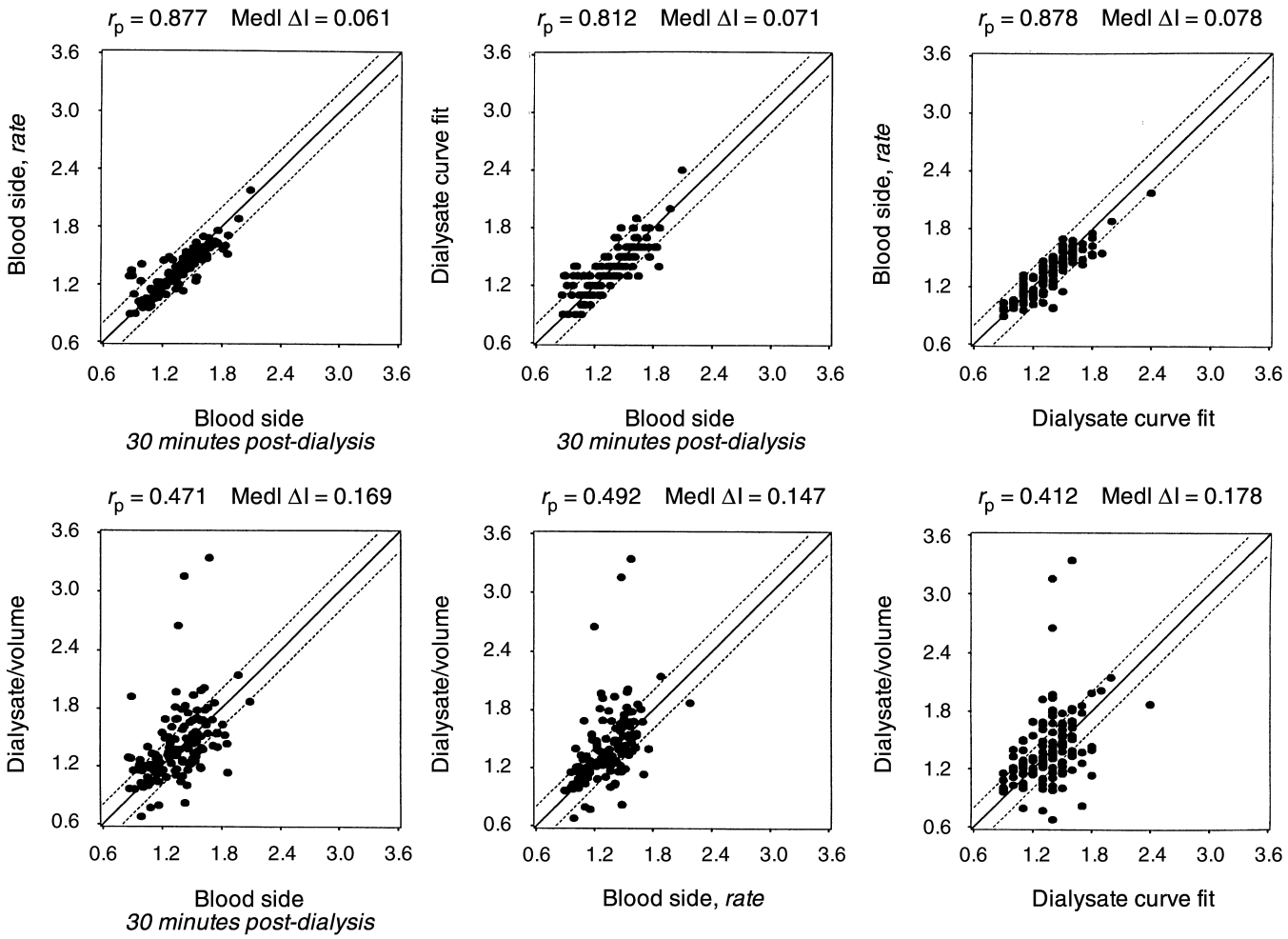

Fig. 2. The source of the data and format of the plots are similar to Figure 1, except that the data points denote equilibrated dialysis dose (eKt/V) instead of SRI. The association of the dialysate/volume method with each of the other three methods is weaker than the associations among the two blood-side methods and the dialysate curve-fit method (Table 3).

the three blood-side and dialysate curve-fit methods than among the three blood-side and dialysate curve-fit methods themselves.

For both SRI and eKt/V, the median algebraic deviation (median Δ) between the dialysate/volume method and the three blood-side and dialysate curve-fit methods was relatively small and was not consistently larger than the median algebraic deviations among the blood-side and dialysate curve-fit methods. This indicates that the poorer agreement between the dialysate/volume method and the other three methods reflects a greater variability rather than a systematic overestimation or underestimation.

Comparison of method reliability based on statistical error analysis

We examined the conditions under which the magnitudes of the errors in SRI from the dialysate/volume method can be expected to be larger or smaller than errors in SRI determined from the blood-side methods by comparing equations 11 and 12. This comparison is simplified by noting that because the blood samples from a particular dialysis are typically processed and sent together to the clinical laboratory and measured on the same laboratory run, the measurement errors in C_0, C_t, and C_{30} will usually be positively correlated. For quality-control samples obtained during the HEMO Study (see **Procedures** section), the correlation between errors in C_0 and C_t was +0.69, $P < 0.001$. Because the blood-based estimates of C_{eq} are directly correlated with C_t (for the rate method) or C_{30} (for the observed 30-minute postdialysis rebound method), it would be expected that the correlation (ρ) between C_0 and $C_{eq(blood)}$ would be positive. Assuming that $\rho \geq 0$ and that eKt/V > 1.0, as is the case for the HEMO Study, it can be shown from Equations 11 and 12 that the CV for the error in SRI using the volume method is greater than the CV of the error in SRI using a blood-based method if

Table 3. Comparisons of equilibrated Kt/V (eKt/V) derived from different methods

Methods compared[a]	Median Δ	Median |Δ|	Spearman R	Pearson R	Concordance R
Blood-side rate equation vs. blood-side reference	−0.034	0.061	0.89	0.88	0.87
Dialysate curve fit vs. blood-side reference	−0.006	0.071	0.83	0.81	0.81
Dialysate curve fit vs. blood-side rate equation	−0.031	0.078	0.88	0.88	0.87
Dialysate/volume vs. blood-side reference	+0.012	0.169	0.59	0.47	0.43
Dialysate/volume vs. blood-side rate equation	+0.033	0.147	0.61	0.49	0.42
Dialysate/volume vs. dialysate curve fit	+0.029	0.178	0.49	0.41	0.37

Data were obtained from 128 Phase II and Phase III modeled dialyses.

[a] For each of the measures, median |Δ|, Spearman R, Pearson R, and Concordance R, the agreement among the three blood-side and dialysate curve fit methods (top three rows) was significantly better ($P < 0.05$) than the agreement of the dialysate/volume method with each of the other three methods (bottom three rows).

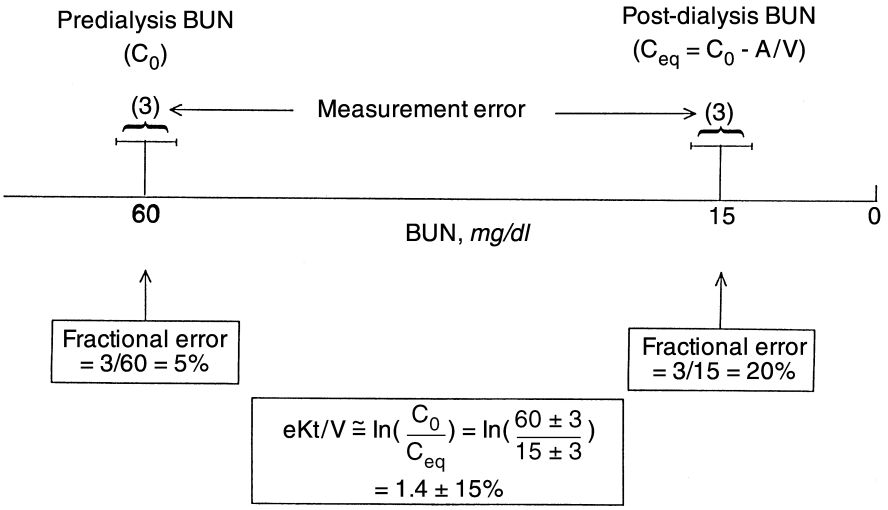

Fig. 3. A simplified fixed volume model with no urea generation showing the error magnification caused by the dialysate/volume method. A/V is the equivalent change in BUN during dialysis calculated by dividing the amount of urea nitrogen removed (A) by the patient's urea volume (V). This example shows a 5% BUN measurement error in the predialysis BUN that is expanded to 15% in the final expression of eKt/V. In contrast to direct measurement, when the equilibrated postdialysis BUN (C_{eq}) is calculated by subtraction of A/V from C_0, fractional errors in the measured values are enlarged.

$$\tau^2(A) > \frac{1}{2} \cdot [\tau^2(C_{eq(blood)}) - \tau^2(C_0) - 2 \cdot \tau^2(V_m)] \qquad \text{(Eq.14)}$$

Expression 14 indicates that even if we neglect errors in V and C_0, A must be determined with a squared CV of less than one half as great as the squared CV in $C_{eq(blood)}$ for the precision of the dialysate/volume method to match the precision of the blood-based methods. Moreover, any variability in the estimates of V or in C_0 reduces the level of precision of the dialysate/volume method compared with that of the blood-based methods. The ratio of the precision of the dialysate/volume method versus the blood-side methods is reduced further if the correlation between the errors for C_0 and $C_{eq(blood)}$ is strictly greater than zero, as will usually be the case.

Illustrations of the effects of errors in C_0 and in A/V_m

One implication of Equation 14 is that an error in C_0 leads to a greater error in eKt/V for the dialysate/volume method than for a blood-based method. The explanation for this phenomenon is illustrated in Figure 3. Comparison of Equations 9 and 10 shows that the only difference between the formulas for SRI for the dialysate/volume and blood-side methods is the dialysate/volume method's use of the term $C_0 - A/V_m$ in place of $C_{eq(blood)}$. Thus, for the dialysate/volume method, $C_0 - A/V_m$ can be viewed as estimating C_{eq}. A straightforward calculation shows that an error of α% in C_0 leads approximately to the same percentage error in $C_{eq(blood)}/C_0$. On the other hand, when C_{eq} is estimated by the difference between C_0 and A/V as in the dialysate/volume method, the error in the estimated C_{eq}/C_0 is approximately $\alpha \cdot SRI/(1 - SRI)$, which is twice as large as the error in the blood-side approach when SRI is 0.667 and three times as large when SRI is 0.750. The larger error results from subtraction of two relatively large numbers (C_0 and A/V) to produce a smaller number (C_{eq}). The same argument indicates that errors in A/V_m also lead to proportionately greater percentage errors in the difference $C_0 - A/V_m$, indicating that the dialysate/volume method may be expected to amplify the effects of errors in A and V_m as well as C_0.

Error analysis for eKt/V

The factor SRI/[eKt/V(1 − SRI)] relating the CV of eKt/V to the CV of SRI in Equation 13 increases as the

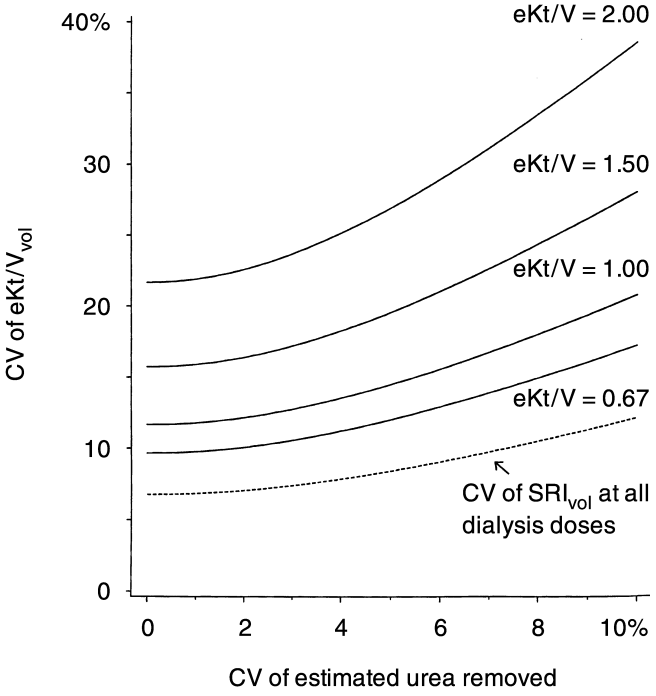

Fig. 4. The coefficient of variation (CV) of eKt/V estimated from the dialysate/volume method increases at high dialysis dose. The dashed line indicates the CV of SRI computed by the dialysate/volume method as a function of the CV of the measurement error in the urea removal [τ(A)]. The solid lines represent the CV of eKt/V computed by the dialysate/volume method as a function of (τA; equation A-2).

dialysis dose increases, indicating that the variability of eKt/V becomes amplified relative to the variability of SRI for high dialysis doses, particularly as SRI approaches its maximum limit of one. This reflects the defined limits of SRI within a narrow range bounded by one at high doses of dialysis, as compared with eKt/V, which has no upper limit. Thus, although comparisons of the performance of different methods in terms of eKt/V will give similar results to comparisons of methods in terms of SRI, for all methods the variability of eKt/V will be higher than the variability of SRI at high dialysis doses. Figure 4, which describes Equation A2 of **Appendix A**, illustrates this point for the dialysate/volume method.

DISCUSSION

Despite the increased precision expected from integration of multiple measurements in the dialysate, the dialysate/volume method used in the HEMO Pilot Study appears to have given significantly less accurate measures of eKt/V and SRI than either the blood-side techniques or the dialysate curve-fit method. We base this conclusion first on the finding that the agreement between the dialysate/volume method and the alternative blood-side and dialysate curve-fit methods was markedly poorer than the agreement among the alternative methods themselves. This reasoning might be criticized on the grounds that the strong agreement between the two blood-side methods ($r = +0.88$, median $|\Delta| = 0.061$ for eKt/V) may reflect coupling of BUN measurement errors so that the comparatively stronger agreement between these two methods may not necessarily indicate a poorer performance of the dialysate/volume method. However, coupling of measurement errors cannot explain the markedly better agreement of the blood-side and the dialysate curve-fit methods (which were based on independent measurements) with each other than with the dialysate/volume method.

The statistical error analyses provided a second set of evidence suggesting a poorer performance of the dialysate/volume method. As shown in equation 14, even if we neglect the error in V_m and C_0, then for the precision of the dialysate/volume method to match the precision of a blood-based method, it would be necessary for the squared CV of the urea removal (A) to be less than one half of the squared CV of the estimate of C_{eq} in the blood-based approach. Any variability in either C_0 or in V_m will add to the advantage of the blood-based methods relative to the dialysis/volume method. Thus, there appears to be an instability of the dialysate/volume method inherent in its mathematical definition, independent of the precision with which urea removal is estimated.

One of the strengths of the dialysate/volume method is its reliance on V. In contrast to clearance (K) and duration of treatment (T_d), V is a physiological parameter considered equivalent to the patient's water volume [29], which should vary little from month to month when measured at the end of dialysis. The known urea volume (V) can be determined from measurements of the predialysis BUN (C_0), the amount of urea removed during dialysis (A), and the equilibrated postdialysis BUN (C_{eq}; equation 1). Because V is relatively constant, compared with C_{eq}, eKt/V, and SRI, it can be repeatedly measured and averaged over many dialysis treatments giving an increasingly accurate figure expressed here as V_m. If V_m can be measured accurately, for example, as the mean of several measurements as was done in this study, the equilibrated postdialysis BUN can be derived from it by measuring A and C_0 (equations 2 and 8). The effective urea clearance or patient clearance can then be derived from single pool analysis of C_0 and C_{eq} using urea kinetic modeling.

In principle, the dialysate/volume method would appear to have other advantages over the traditional fitting of predialysis and postdialysis or multiple intradialysis and postdialysis BUN measurements to a model of urea kinetics. There are no constraints imposed by a mathematical model, and once V_m is determined, there is no need to measure the postdialysis BUN, sometimes called

a "moving target." The postdialysis BUN is subject to error due to potential access recirculation, to the ever-present rebound from dialysis disequilibrium, to dilution with solutions often infused at the end of dialysis, and to inaccuracies of measurement by clinical laboratories unaccustomed to measuring low concentrations with high precision. In addition, even experienced technicians will occasionally draw the postdialysis blood sample from the wrong (venous return) port, falsely lowering the postdialysis BUN and causing an overestimation of Kt/V. Ideally, the postdialysis BUN should be measured at equilibrium, but this requires a delay of 30 to 60 minutes after stopping dialysis. Delaying each patient's dialysis on a repeated routine basis is not feasible in most dialysis centers.

However, as illustrated in Figure 3, a key difficulty with the dialysate/volume method is in its derivation of the equilibrated postdialysis BUN (C_{eq}) from mathematical subtraction of two relatively precise but similar-in-magnitude numbers, the predialysis body urea nitrogen content and the urea nitrogen removed during dialysis (equation 2). Thus, relatively small errors in either C_0 or A/V_m lead to comparatively large errors in the difference, C_{eq}, particularly at high doses of dialysis when C_{eq} is smallest. By contrast, blood-side methods avoid this error magnification by directly measuring a BUN at the end of dialysis. For example, with the rate adjustment method (equation 5), C_{eq} is derived from spKt/V, which is calculated from the measured values of C_t and C_0. This study shows that the potential inaccuracies in C_t listed earlier here had less of an impact than the subtraction error shown in Figure 3. Because the dialysate concentration profile mirrors the blood concentration profile, the dialysate curve-fitting technique also appears to have avoided the difficulties associated with the dialysate/volume method and produced estimates of eKt/V and SRI with similar variability to the blood-side methods. In principle, the inclusion of multiple dialysate concentrations should enhance the precision of the dialysate curve-fitting technique.

As shown in equation 13, the CV of eKt/V due to measurement error is substantially greater than the CV of SRI at high doses of dialysis. The relationship is independent of the methodology used so that a method that leads to a more precise estimate of SRI will also lead to a more precise estimate of eKt/V. The smaller CV of SRI reflects its definitional restriction below one, which constrains its range at high doses of dialysis. Thus, the greater CV of eKt/V than SRI at high doses of dialysis is a consequence of the different ranges of these measures rather than a greater accuracy for the SRI. The SRI's direct interpretation as the fraction of urea removed during dialysis is intuitively appealing, and the SRI is a particularly natural index for dialysate methods. However, it suffers from lack of immediate applicability for determination of dialysis prescriptions because it cannot be directly related to a clearance, to blood and dialysate flow, or to treatment time like eKt/V.

In conclusion, although the dialysate/volume method is attractive for other reasons, an empiric and theoretical analysis of sensitivity showed that it caused much larger errors in measurement of both SRI and eKt/V than blood-side methods. Consequently, the dialysate/volume method had to be dropped from consideration for use in the full scale HEMO Study. In general, methods for quantitating the dose of dialysis based on the change in measured urea concentrations during dialysis (in blood or in dialysate) appear to have an inherent advantage in being more precise than methods that are limited to measurement of fractional urea removal.

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APPENDIX A

By combining equations 13 and 11, we see that the CV for eKt/V based on the dialysate/volume method is as follows:

$$\tau(eKt/V_{vol}) \cong \frac{SRI}{eKt/V \cdot (1 - SRI)} \times \sqrt{\tau^2(A) + \tau^2(C_0) + \tau^2(V_m)} \qquad \text{(Eq. A1)}$$

This expression shows how the effects of errors in A, C_0, and V_m on eKt/V are amplified at high doses of dialysis. Based on the pilot study quality-control data, in which samples were split and sent to the central laboratory on different days, the bias-corrected maximum likelihood estimation of $\tau(C_0)$ is 0.025. Based on the observed variation in V during the pilot study, phase I baseline, we can similarly estimate the CV of the individual Vs as 0.110 so that the CV of V_m is $0.110/\sqrt{3}$, or 0.063. Substituting these results into equation A1 shows that under the conditions of the HEMO pilot study:

$$\tau(eKt/V_{Vol}) \cong \frac{SRI}{eKt/V \cdot (1 - SRI)} \times \sqrt{\tau^2(A) + 0.0046} \qquad \text{(Eq. A2)}$$

APPENDIX B

Statistical background

The statistical sensitivity analysis is based on the following: Let $X_1, X_2, \ldots, X_k$ be random variables with means $\mu_1, \mu_2, \ldots, \mu_k$, and variances $\sigma_1^2, \sigma_2^2, \ldots, \sigma_k^2$, and let ρ_{ij} denote the correlation between X_i and X_j, $i \neq j$. If $\sigma_1^2, \sigma_2^2, \ldots, \sigma_k^2$ are small, and f is a smooth function of $X_1, X_2, \ldots, X_k$, then

$$E[f(X_1, X_2, \ldots, X_k)] \cong f(\mu_1, \mu_2, \ldots, \mu_k), \qquad \text{(Eq. B1)}$$

and

$$Var[f(X_1, X_2, \ldots, X_k)] \cong \sum_{i=1}^{k} \left(\left. \frac{\partial f}{\partial X_i} \right|_{X_i = \mu_i} \right)^2 \cdot \sigma_i^2 + \sum_{i<j} 2 \cdot \left(\left. \frac{\partial f}{\partial X_i} \right|_{X_i = \mu_i} \right) \cdot \left(\left. \frac{\partial f}{\partial X_i} \right|_{X_i = \mu_j} \right) \cdot \sigma_i \cdot \sigma_j \cdot \rho_{ij} \qquad \text{(Eq.B2)}$$

Here, $E[f(X_1, X_2, \ldots, X_k)]$ represents the mean value of $f(X_1, X_2, \ldots, X_k)$, and Var $[f(X_1, X_2, \ldots, X_k)]$ represents the variance, or the squared standard deviation, of $f(X_1, X_2, \ldots, X_k)$. If the X_i are not correlated, then $Var[f(X_1, X_2, \ldots, X_k)]$ is approximated by the sum of the products of the squared partial derivatives of f with respect to the X_i and the variances of the X_i. If f is a function of a single random variable X_1, then equation B2 reduces to

$$Var[f(X_1)] \cong \left(\left. \frac{\partial f}{\partial X_i} \right|_{X_i = \mu_i} \right)^2 \cdot \sigma_1^2$$

To apply equations B1 and B2 to derive Equations 11, 12, and 13, the σ_i are identified with variability due to measurement error, and the μ_i are regarded as the "true values" of the respective quantities that would have been obtained in the absence of measurement error.

To avoid cumbersome notation, we will take advan-

tage of the fact that the variability of the investigated quantities is small compared with their mean values and take the liberty of writing C_0, A, V_m, and C_{eq} in place of the mean values of these quantities when applying Equations B1 and B2.

Derivation of equations 11 and 12

Let $SRI_{Vol} = f(A, C_0, V_m) = A/(C_0 \cdot V_m)$. Then,

$$\frac{\partial f}{\partial A} = \frac{1}{C_0 \cdot V_m}, \frac{\partial f}{\partial C_0} = \frac{-A}{C_2^0 \cdot V_m},$$

and

$$\frac{\partial f}{\partial V_m} = \frac{-A}{C_0 \cdot V_m^2}.$$

Because the measurement errors in A, C_0, and V_m are statistically independent and hence not correlated with one another, Equation B2 gives:

$$\begin{aligned} \text{Var}\,(SRI_{Vol}) &\cong \frac{1}{C_0^2 \cdot V_m^2}\,\sigma^2(A) + \frac{A^2}{C_0^4 \cdot V_m^2} \cdot \sigma^2\,(C_0) \\ &+ \frac{A^2}{C_0^2 \cdot V_m^4} \cdot \sigma^2(V_m) \\ &= \frac{A^2}{C_0^2 \cdot V_m^2} \cdot [\tau^2(A) + \tau^2(C_0) + \tau^2(V_m)]. \end{aligned}$$

Dividing both sides of this Equation by $\frac{A^2}{C_0^2 \cdot V_m^2}$ and taking the square root gives Equation 11.

To obtain Equation 12, write $C_{eq} = C_{eq(blood)}$, and $SRI_{blood} = g(C_{eq}, C_0) = 1 - \frac{C_{eq}}{C_0}$. Then

$$\frac{\partial g}{\partial C_0} = \frac{C_{eq}}{C_0^2}, \frac{\partial g}{\partial C_{eq}} = -\frac{1}{C_0}, \text{ and } \frac{\partial g}{\partial C_0} \cdot \frac{\partial g}{\partial C_{eq}} = -\frac{C_{eq}}{C_0^3}.$$

Equation B2 therefore implies

$$\begin{aligned} \text{Var}(SRI_{blood}) \cong\ & \frac{C_{eq}^2}{C_0^4} \cdot \sigma^2(C_0) + \frac{1}{C_0^2} \cdot \sigma^2(C_{eq}) \\ & - \frac{2 \cdot C_{eq}}{C_0^3} \cdot \sigma(C_0) \cdot \sigma(C_{eq}) \cdot \rho(C_0, C_{eq}). \end{aligned}$$

Equation 12 now follows by dividing both sides of this expression by $(C_0 - C_{eq})^2/C_0^2$ and taking the square root.

Derivation of Equation 13

To obtain Equation 13, write $eKt/V = -\ln(1 - SRI) = h(SRI)$, say. Then

$$\frac{\partial h}{\partial SRI} = \frac{1}{1 - SRI},$$

and by Equation B2,

$$\text{Var}(eKt/V) \cong \frac{1}{(1 - SRI)^2} \cdot \sigma^2\,(SRI).$$

Hence,

$$\tau^2(eKt/V) \cong \left(\frac{SRI}{1 - SRI}\right)^2 \cdot \left(\frac{1}{eKt/V}\right)^2 \cdot \tau^2\,(SRI),$$

from which Equation 13 follows.