Factors that Affect Postdialysis Rebound in Serum Urea Concentration, Including the Rate of Dialysis: Results from the HEMO Study

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Abstract. Previous studies have suggested that postdialysis urea rebound is related to K/V, the rate of dialysis, but a systematic analysis of factors that affect rebound has not been reported. With the use of 30-min and, in a subset, 60-min postdialysis samples, postdialysis urea rebound was measured to (*1*) determine how well previously proposed equations based on the rate of dialysis (K/V) predict rebound in a large sample of patients with varying characteristics, (*2*) determine whether other factors besides K/V affect rebound, and (*3*) estimate more precise values for coefficients in prediction equations for rebound. Rebound was calculated relative to both immediate and 20-s postdialysis samples to study early components of rebound unrelated to access recirculation. The equilibrated Kt/V (eKt/V) computed by fitting the two-pool variable volume model to the 30-min postdialysis sample agreed well with eKt/V based on the 60-min postdialysis sample. Using the pre-, post-, and 30-min postdialysis samples for 1245 patients with arteriovenous (AV) accesses, the median intercompartmental mass transfer coefficient (Kc) was 797 ml/min for rebound computed relative to the 20-s postdialysis samples and 592 ml/min relative to the immediate postdialysis samples. K/V was the strongest predictor of rebound among 22 factors considered. Other factors associated with greater rebound for 1331 patients using AV accesses or venous catheters included access type, black race, male gender, absence of congestive heart failure, greater age, ultrafiltration rate, and low predialysis or intradialysis systolic BP. Equations of the form eKt/V = single-pool Kt/V − B × (K/V) were fit to the data. With AV access, the optimum values for the slope term (B) were 0.39 and 0.46 (in h^{-1}) for single-pool Kt/V calculated based on 20-s postdialysis or immediate postdialysis samples, respectively. For patients using venous catheters, the respective values for B were 0.22 and 0.29. Postdialysis urea rebound can be predicted with acceptable accuracy from a postdialysis sample using a zero-intercept, K/V-based rate equation. Several patient or treatment-specific factors predict enhanced or reduced rebound. Rate equation slope coefficients for K/V of 0.39 (AV access) and 0.22 (venous access) are proposed when a 15- to 20-s slow-flow method is used to draw the postdialysis blood. Slightly higher K/V slope coefficients (0.46 and 0.29, respectively) should be used if a shorter (*e.g.*, 10 s) slow-flow period is used.

Postdialysis urea rebound is thought to have three components: (*1*) access recirculation, (*2*) cardiopulmonary recirculation (CpR), and (*3*) entry of urea from poorly accessible tissue compartments that were not well depurated during the dialysis treatment. The effects of access recirculation on the postdialysis blood sample are normally obviated by obtaining this sample using a slow-flow technique (50 to 100 ml/min) for sampling the postdialysis blood 15 s or so after dialysis (1,2). CpR is due to rapid partial closure of the arteriovenous (AV) urea gradient after cessation of dialysis, as cleared blood is no

longer being returned to the heart. If the blood is being sampled from an arterial site, then an early rise in urea concentration will be noted as early as 10 to 15 s after dialysis has ceased, as a result of this blood pool re-equilibration effect. By 1 min or so after dialysis, the effect of CpR should have largely dissipated (3).

The third component of postdialysis rebound is thought to be due to release of urea from sites where it had been sequestered during dialysis, as a result of a low rate of perfusion relative either to urea stores or to some tissue barrier (*e.g.*, the cell membrane). This third phase of urea rebound is thought to be largely complete by 30 min and finished by approximately 60 min after dialysis. Third-phase rebound theoretically depends on the size of the sequestered urea pool (thought to include muscle) and the extent to which urea removal from this tissue pool has been impeded during dialysis by virtue of reduced blood flow (4–6).

Recently, a popular approach for accounting for the effect of postdialysis rebound on dialysis dose has been to estimate the

equilibrated Kt/V (eKt/V) as a linear function of the single-pool Kt/V (spKt/V) and the rate of dialysis (K/V). For dialysis using an AV access, the equation states that eKt/V = spKt/V − 0.6 × K/V + 0.03. The term K/V is the rate of dialysis expressed as spKt/V units per hour (6). A similar rate equation for use with venous access, where eKt/V = spKt/V − 0.47 × K/V + 0.02, was also proposed and simply represents the same total rebound with the CpR component removed (6). According to the rate equations, substantial postdialysis urea rebound can be anticipated when high-efficiency dialysis is delivered, particularly to a smallish patient, because then K/V may be high. The major advantage of the rate equation is that the eKt/V can be predicted on the basis of a postdialysis sample taken very soon after the end of dialysis.

The coefficients (slope as well as intercept) in these rate equations were derived from an empiric set of dialysis prescriptions in which theoretical rebound was calculated using a regional blood-flow model of urea kinetics. The steepness levels of the slope coefficients, in particular, are sensitive to cardiac output as well as to fractional blood flow to and volume of a postulated "low-flow" compartment (6). The regional blood-flow modeling parameters used in these analyses were derived from organ volumes, urea contents, and blood perfusion rates obtained from the physiology literature and from cardiac output data measured in a limited set of hemodialysis patients. Thus, the optimum values for these rate equation coefficients remain a matter of some uncertainty.

On the basis of a preliminary validation of the accuracy of the AV rate equation during a pilot study (7), this equation was used to monitor dialysis adequacy on a monthly basis during the Full-Scale HEMO Study (8,9). Further validation of the AV and venous rate equations, described here, was included in the design of the HEMO Study, based on formal urea modeling done with the aid of delayed postdialysis serum urea samples at a single session 4 mo into the study.

We had three primary objectives: (1) to determine how well first-order rate equations based on the rate of dialysis (K/V) predict urea rebound in a large sample of dialysis patients with widely varying characteristics, (2) to determine whether other patient-related or treatment-related factors affect the magnitude of rebound, and (3) to take advantage of the large sample size of the HEMO trial to determine more precise values for coefficients in the prediction equations for rebound that might be appropriate for general application.

Materials and Methods

The HEMO Study was a randomized, multicenter clinical trial designed to study the effects of dialysis dose and membrane flux on survival and other outcomes (8,9). Patients were randomized using a 2 × 2 factorial design to a target eKt/V of either 1.05 or 1.45 and use of either low-flux or high-flux membranes. Entry criteria included a three-treatment-per-week dialysis schedule for at least 3 mo, age 18 to 80 yr, residual renal clearance <1.5 ml/min per 35 L of urea volume, and anticipated ability to achieve a target eKt/V of 1.45 during a 4.5-h dialysis (8,9). A total of 1846 patients were randomized between 1995 and 2001 in 72 dialysis units affiliated with 15 clinical centers in the United States.

After randomization, routine kinetic modeling for monitoring adherence to the eKt/V targets was performed monthly based on predialysis blood urea nitrogen (BUN) and a postdialysis BUN drawn 20 s after slowing the blood pump to <80 ml/min (these samples hereafter will be termed "slow-flow inlet" samples). Extended kinetic modeling sessions done 4 mo after randomization included seven blood draws: (1) predialysis, (2) 1 h full-flow inlet, (3) 1 h full-flow outlet, (4) 1 h slow-flow inlet, (5) immediate postdialysis full-flow inlet, (6) 20 s postdialysis slow-flow inlet, and (7) 30 min postdialysis. In a subset of patients, two additional blood samples were drawn at 2 and 60 min after the end of dialysis. BUN was measured at a central laboratory (Spectra East, Rockleigh, NJ).

Serum creatinine was recorded from local laboratory measurements, BP and the occurrence of intradialytic cramping were recorded from the dialysis run sheets, and use of antihypertensive medications was extracted from the patient charts. Total ultrafiltration during the dialysis session and the average ultrafiltration rate (in ml/min) were computed from recorded weight loss during the dialysis session and from the ratio of the weight loss to the treatment time, respectively. Patients were classified as diabetic or as having congestive heart failure when they had an index of disease severity score of 1 or greater on the Index of Coexisting Disease (10), which is a standardized instrument for evaluating comorbidity in dialysis patients based on review of medical records.

Among 1846 randomized patients, 1590 remained in the study at 4 mo and provided the predialysis, full- and slow-flow postdialysis, and 30-min postdialysis blood samples. Additional exclusions were 139 because the exact time of the 30-min postdialysis sample was not recorded, 37 because of blood-drawing errors or >15 min of dialysis treatment interruption time, 28 because the curve-fit algorithm used to estimate the equilibrated postdialysis BUN for the reference method did not converge, and 55 because of >15% access recirculation. Access recirculation was computed as 100 × (S-F)/(S-O) where S, F, and O were urea concentrations drawn at 1 h under conditions of slow-flow inlet, full-flow inlet, and full-flow outlet, respectively (11).

After these exclusions, 1331 patients were retained, including 1245 using AV accesses, 70 using venous catheters, and 16 whose access could not be classified. A total of 156 of the 1245 on AV accesses participated in the substudy with additional BUN at 2 and 60 min postdialysis, as did 13 of the 70 patients on venous catheters.

Methods for Estimating eKt/V

Three-BUN Curve-Fit to 20 S and 30 Min Postdialysis Samples. A two-pool variable volume model of urea kinetics (7) was fit to the predialysis BUN, the 20-s postdialysis BUN adjusted for CpR (3,7), and the 30-min postdialysis BUN. The 20-s postdialysis BUN was adjusted for CpR by dividing by the estimated AV urea ratio (Fcp), which was estimated as described previously (7). *In vivo* blood water dialyzer clearances (Kd) were estimated from dialyzer-specific *in vivo* K_0A values (derived from multiple measurements of cross-dialyzer urea clearance) and adjusted for blood-flow errors as a result of prepump pressure effects as described previously (12,13), with appropriate adjustments for blood water concentration (0.894) and ultrafiltration (14). The *in vivo* Kd was then multiplied by Fcp to account for its acting on the arterial circulation during dialysis, whereas the intradialytic profile being modeled during dialysis was that of venous blood. The adjusted Kd, the predialysis BUN, an initial single-pool estimate of the urea generation rate (G), and the ultrafiltration rate were then used as inputs along with trial estimates of the intercompartment transfer coefficient (Kc) and total urea volume (V) to numerically solve the two-pool variable volume model to predict

values for the 20-s and 30-min postdialysis BUN values. The ratio of the intracellular and extracellular volumes was assumed to be 2 to 1 at the end of dialysis, all fluid removal was assumed to occur from the extracellular compartment, and urea generation was assumed to appear first in the extracellular compartment. Optimal values of Kc and V were then derived using numerical methods to produce predicted BUN with the minimum sum of squared deviations from the actually observed BUN values (7). On the basis of the optimal Kc and V, the equilibrated postdialysis BUN (Ceq) adjusted for the initial single-pool G was estimated. This estimate of Ceq was then substituted for the postdialysis BUN in Depner and Cheer's two-BUN algorithm (14) to compute eKt/V and an updated equilibrated estimate of the urea generation rate (eG). The full procedure described above was then repeated using the updated eG in place of the initial single-pool G as an input parameter. The final value of eKt/V produced by this procedure is denoted $eKt/V_{30|20s}$.

Other Curve-Fit Estimates of eKt/V. The three-BUN curve-fit procedure described above was also applied to obtain alternative estimates of Ceq and eKt/V in the full 4-mo cohort based on the predialysis BUN, the immediate postdialysis BUN, and the 30-min postdialysis BUN; and in the intensive substudy based on the predialysis BUN, the 2-min postdialysis BUN, and the 60-min postdialysis BUN. The 2-min postdialysis BUN in the substudy was assumed to include 100% of the rebound from cardiopulmonary recirculation. These curve-fit estimates of eKt/V are denoted $eKt/V_{30|0s}$ and eKt/V_{60}, respectively.

Existing Rate Adjustment

The rate adjustment formulas for estimated eKt/V from the rate of dialysis (K/V) and the spKt/V described by Daugirdas and Schneditz (6) are as follows: $eKt/V_{rate.orig} = spKt/V − 0.6 × (spKt/V)/T + 0.03$ (for AV accesses) and $eKt/V_{rate.orig} = spKt/V − 0.47 × (spKt/V)/T + 0.02$ (for venous catheters), where T represents the duration of dialysis in hours. The spKt/V in these equations was computed from the Depner and Cheer two-BUN equations (14) using the estimated *in vivo* Kd as described above but without application of the Fcp adjustment. These rate equations were evaluated first with spKt/V computed based on the predialysis and the slow-flow postdialysis BUN (denoted $spKt/V_{20s}$) and again with spKt/V computed from the predialysis and immediate full-flow postdialysis BUN (denoted $spKt/V_{0s}$).

Data Analysis

Comparisons of quantitative variables between two groups are based on pooled or unpooled *t* tests as appropriate for approximately normally distributed variables and on Wilcoxon rank-sum tests for nonnormal variables.

Strategy for Evaluating Estimates of eKt/V

We first used the subset with 60-min postdialysis samples to validate the estimates $eKt/V_{30|20s}$ and $eKt/V_{30|0s}$ by examining their agreement with eKt/V_{60}. Subsequently, $\Delta Kt/V_{20s} = spKt/V_{20s} − eKt/V_{30|20s}$ and $\Delta Kt/V_{0s} = spKt/V_{0s} − eKt/V_{30|0s}$ were computed as measures of rebound and related to K/V and other variables in the full data set.

Statistical Analyses

The agreement between different measures of eKt/V was evaluated by the Pearson correlation coefficient (R) to evaluate linear association, the median algebraic difference (median Δ) and the mean algebraic difference (mean Δ) to evaluate systematic bias, and median absolute difference (median $|\Delta|$) and the concordance correlation coefficient Rc to evaluate overall agreement.

Multiple regression using robust M-estimation with the bisquare weight function (15) was used to relate $\Delta Kt/V_{20s}$ and $\Delta Kt/V_{0s}$ to K/V, type of access (AV *versus* venous catheter), clinical center, and the remaining factors listed in Table 1 (for a total of 22 potential predictor variables). Many of these factors were chosen on the basis of a postulated role for muscle mass and regional blood flow to affect urea rebound (4–6).

A backward selection procedure was used to determine a set of independent predictors of either $\Delta Kt/V_{20s}$ or $\Delta Kt/V_{0s}$. The backward selection was performed by first conducting separate regressions of $\Delta Kt/V_{20s}$ and $\Delta Kt/V_{0s}$ *versus* all of the indicated factors, and then recursively deleting that factor for which the minimum *P* value between the two regressions was the largest among the factors remaining in the model. This procedure was repeated until $P < 0.05$ for both $\Delta Kt/V_{20s}$ and $\Delta Kt/V_{0s}$ for all remaining factors.

Optimal coefficients in rate equations of the form $eKt/V = spKt/V − B1 × K/V + B2$ were estimated separately in AV and venous access by estimating intercepts and slopes in robust regressions of $\Delta Kt/V_{20s}$ and $\Delta Kt/V_{0s}$ *versus* K/V. Separate robust regression equations were estimated assuming 0 intercepts.

Standard errors in the robust regression analyses were computed by the bootstrap method (16) with 800 replications. Statistical analyses were carried out using SAS version 8 and S-plus version 3.1.

Results

Validation of the Use of 30-Min Postdialysis BUN (Substudy)

There was close agreement between eKt/V determined using the 60-min sample (eKt/V_{60}) and the estimates of eKt/V determined by fitting the two-pool model to extrapolate the 30-min BUN. For the 156 substudy patients on AV accesses, the Pearson correlation coefficient between $eKt/V_{30|20s}$ and eKt/V_{60} was $R = 0.970$, and the median Δ between the two eKt/V values was 0, indicating no systematic bias. Similar agreement was observed between eKt/V_{60} and $eKt/V_{30|0s}$ ($R = 0.964$, median $|\Delta| = 0.029$). For the 13 substudy patients on venous catheters, agreement was also high between eKt/V_{60} and $eKt/V_{30|20s}$ ($R = 0.981$, median $|\Delta| = 0.035$) and between eKt/V_{60} and $eKt/V_{30|20s}$ ($R = 0.984$, median $|\Delta| = 0.022$).

Patient and Treatment Characteristics

Characteristics of the 1331 patients in the full 4-mo data set are summarized in Table 1, with patients in both dose groups combined.

Predictors of Urea Rebound

The final models from the backward selection procedure for $\Delta Kt/V_{20s}$ and $\Delta Kt/V_{0s}$ are summarized in Table 2. The most powerful predictor of urea rebound (expressed as $\Delta Kt/V$) was the rate of dialysis (K/V). After K/V, the factors associated with the largest differences in $\Delta Kt/V$ were venous accesses (associated with an approximately 0.06 Kt/V unit smaller $\Delta Kt/V$ than AV accesses), and black race, which was associated with an approximately 0.03 to 0.04 greater $\Delta Kt/V$ than nonblacks. Male gender, greater age, and a higher relative ultrafiltration rate were associated with greater rebound, as was a lower minimum systolic BP during dialysis and a lower

Table 1. Characteristics of 4-month sample[a]

Label	All 4-Month Patients ($N = 1331$)	AV Accesses ($N = 1245$)	Venous Catheters ($N = 70$)
K/V (h^{-1})	0.45 ± 0.08	0.46 ± 0.08	0.42 ± 0.10
Age (yr)	57.8 ± 14.1	57.8 ± 14.1	57.8 ± 13.8
% Diabetic	43.4	42.9	45.7
% Black	62.4	63.1	44.3
% Female	55.7	54.3	74.3
% History of CHF	38.9	37.9	57.1
Anthropometric V (L)[b]	35.2 ± 6.1	35.4 ± 6.1	31.8 ± 5.3
Serum creatinine (mg/dl)	10.3 ± 2.9	10.4 ± 2.9	9.1 ± 2.8
Predialysis SBP (mmHg)	152.9 ± 25.7	153.0 ± 25.6	150.4 ± 27.6
Predialysis DBP (mmHg)	81.7 ± 15.3	81.8 ± 15.3	80.0 ± 16.3
Δ Min SBP (mmHg)[c]	-34.7 ± 25.6	-34.9 ± 25.8	-31.1 ± 23.2
Δ Min DBP (mmHg)[c]	-15.4 ± 15.9	-15.5 ± 16.0	-12.7 ± 14.0
Total Uf/Vant (% per dialysis)[d]	8.4 ± 3.5	8.5 ± 3.5	7.8 ± 3.6
Qf/Vant (% per h)[e]	2.5 ± 1.1	2.5 ± 1.1	2.3 ± 1.1
% With hypotensive symptoms[f]	20.8	21.4	11.4
% Reporting cramping[f]	9.5	9.7	7.1
% on ACEi	24.3	24.5	23.2
% on β-blocker	28.1	27.9	31.9
% on Calcium channel blocker	47.9	48.3	43.5
% on α-1 antagonist	5.3	5.5	0.0

[a] Data are mean $\pm$ SD or %. CHF, congestive heart failure; SBP, systolic BP; DBP, diastolic BP; ACEi, angiotensin-converting enzyme inhibitor.
[b] Computed by the Watson formula ((31)).
[c] Minimum BP recorded during the treatment minus the predialysis value.
[d] Ratio of weight loss during treatment (Uf) to the Watson V (Vant), expressed as %.
[e] Ratio of ultrafiltration rate per hour (Qf) to the Watson V (Vant), expressed as %.
[f] Hypotensive symptoms and cramping reported during dialysis.

predialysis systolic BP. The presence of congestive heart failure was associated with a smaller amount of rebound. All of these terms operated concordantly whether the analysis was based on the 20-s postdialysis sample or the immediate 0-s postdialysis sample.

Modeling Results: spKt/V and eKt/V

Modeling results for the 1245 patients on AV accesses are shown in Table 3. The mean spKt/V in the standard dose arm at the 4-mo session was 1.34, *versus* 1.74 in the high-dose arm. The mean $eKt/V_{30|20s}$ using the 30-min postdialy-

Table 2. Predictors of postdialysis urea rebound ($\Delta Kt/V$)

	20-Second Postdialysis ($\Delta Kt/V_{20s}$)				0-Second Postdialysis ($\Delta Kt/V_{0s}$)			
	Regression Coefficient[a]	SE	T Ratio	*P* Value	Regression Coefficient[a]	SE	T Ratio	*P* Value
K/V ratio (per h^{-1})	0.450	0.033	13.6	<0.001	0.52	0.038	13.5	<0.001
Venous access	-0.057	0.011	-5.43	<0.001	-0.055	0.012	-4.78	<0.001
Black	0.029	0.006	5.37	<0.001	0.037	0.006	6.46	<0.001
Male	0.012	0.005	2.34	0.019	0.016	0.006	2.77	0.006
History of CHF	-0.013	0.005	-2.48	0.013	-0.012	0.005	-2.23	0.026
Age (per 10 yr)	0.0042	0.0016	2.63	0.008	0.0045	0.0018	2.59	0.010
Δ Min SBP (per 10 mmHg)	-0.0053	0.0011	-4.74	<0.001	-0.0069	0.0011	-6.21	<0.001
Predialysis SBP (per 10 mmHg)	-0.0035	0.0011	-3.03	0.002	-0.0052	0.0012	-4.47	<0.001
Qf/Vant (per % per h)	0.0061	0.0021	-2.89	0.004	0.0079	0.0026	3.07	0.002

[a] Regression coefficients indicate the mean increase in $\Delta Kt/V$ associated with an increase in the predictor variables by the indicated units. The coefficients for the dichotomous factors venous access, black race, male gender, and history of CHF indicate the difference in mean $\Delta Kt/V$ with these factors present *versus* the mean $\Delta Kt/V$ with the factor absent. Each regression coefficient is adjusted for the other terms in the model and for clinical center, which was also a significant predictor of both $\Delta Kt/V_{20s}$ and $\Delta Kt/V_{0s}$.

Table 3. Treatment parameters and modeling results for patients on AV accesses[a]

	Standard Dose Group (n = 622)			High-Dose Group (n = 623)			P Value (High *versus* Standard)[b]
	Median	Mean	SD	Median	Mean	SD	
Blood flow rate (ml/min)	328	329	74	430	417	55	<0.001
Dialysate flow rate (ml/min)	600	638	138	800	711	118	<0.001
Dialyzer clearance Kd (ml/min)	220	219	28	254	253	20	<0.001
Treatment time (min)	186	190	24	217	219	25	<0.001
K/V^1 (h^{-1})	0.42	0.43	0.07	0.48	0.48	0.08	<0.001
URR (%)[c]	66.7	66.6	4.4	76.2	75.9	3.8	<0.001
spKt/V[c]	1.33	1.34	0.17	1.74	1.74	0.20	<0.001
$eKt/V_{30|20s}$	1.14	1.15	0.16	1.55	1.55	0.20	<0.001
$eKt/V_{30|0s}$	1.14	1.15	0.17	1.55	1.55	0.21	<0.001
$eKt/V_{rate.orig}$[c]	1.11	1.11	0.14	1.47	1.48	0.16	<0.001
Unadjusted Vsp (L)[c]	30.9	31.5	6.76	31.9	32.4	6.52	0.014
Vdp (curve fit)[c]	31.2	31.6	6.91	30.6	31.1	7.14	0.122

[a] URR, urea reduction ratio; Vsp, single pool urea volume; Vdp, estimated double pool urea volume; BUN, blood urea nitrogen.

[b] *P* values for differences in mean values between dose groups.

[c] Calculated using the 20-s postdialysis BUN.

[d] eKt/V $V_{30|0}$ calculated using the 0 second postdialysis BUN.

sis BUN was 1.15 and 1.55 in the standard-dose and high-dose groups, respectively.

The values for the estimated intercompartment transfer coefficient Kc depended on whether rebound was counted from the 20-s slow-flow postdialysis sample (median Kc = 797 ml/min, 25th percentile = 501 ml/min, 75th percentile = 1492 ml/min) or from the full-flow postdialysis sample (median Kc = 592 ml/min, 25th percentile = 399, 75th percentile = 989 ml/min). This range of Kc values is similar to that reported elsewhere (17–20).

The last two rows of Table 2 summarize single-pool and double-pool estimates of the modeled urea distribution volume. As detailed previously (21), the single-pool V seems to overestimate the double-pool V based on the curve-fit solution in the high-dose group (mean single-pool V = 32.4 L *versus* mean double-pool V = 31.1 L), whereas the mean single-pool and double-pool volumes are similar in the standard dose group.

Percentage of Rebound

The percentage of rebound after full equilibration compared with the postdialysis BUN is shown in Figure 1 for patients using AV accesses and venous catheters, respectively. For both AV accesses and catheters, the median percentage of rebound to the equilibrated postdialysis BUN was greater when computed from the 0-s (immediate) postdialysis BUN sample than when computed from the 20-s postdialysis sample, and the median percentage of rebound between the 0-s and 20-s samples was significantly greater than 0 ($P < 0.001$ for both types of access). The occurrence of some rebound in the 20-s sample explains the difference between the median values of Kc when the 0-s and 20-s postdialysis samples were used.

Estimation of Rebound Using the Original Rate Equation

The rate equation used in the experimental design slightly overestimated rebound, leading to an underestimation of eKt/V (Figure 2). When the rate equation was determined using the 20-s postdialysis BUN, the median $eKt/V_{rate.orig}$ was 1.11 *versus* a median $eKt/V_{30|20s}$ of 1.14. In the high-dose group, the median values of $eKt/V_{rate.orig}$ and $eKt/V_{30|20s}$ were 1.47 *versus* 1.54. The median differences between the two eKt/V values were −0.055 and −0.077 in the standard and high-dose groups, respectively. The median biases were smaller when the rate adjustment was based on the immediate postdialysis sample; the median differences between $eKt/V_{rate.orig}$ computed using the immediate postdialysis BUN and $eKt/V_{30|20s}$ were −0.032 and −0.041 in the standard and high-dose arms, respectively.

Although the overestimation of rebound by the rate equation resulted in higher actual eKt/V levels than the targets of 1.05 and 1.45, this overestimation did not adversely affect the separation of eKt/V between the dose groups because the overestimation was similar or slightly greater in the high-dose compared with the standard-dose group. The investigators therefore did not reduce the target dialysis dose levels, because doing so would have resulted in some patients having urea reduction ration (URR) and spKt/V values below DOQI guidelines.

Alternative Rate Equations for General Use

As described in Materials and Methods, we used robust regression of $\Delta Kt/V_{20s} = spKt/V_{20s} - eKt/V_{30|20s}$ on the ratio K/V to develop revised rate equations. The estimated values (±SE) of the intercept and slope coefficients were as follows:

% Rebound by Type of Access
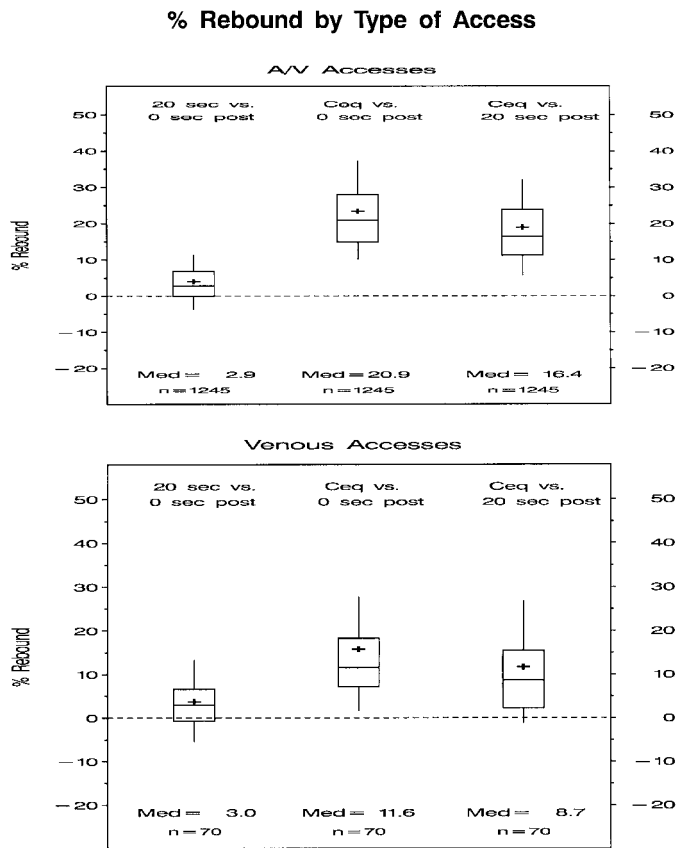
Box plots show 10th, 25th, 50th, 75th and 90th percentiles and mean (+).

Figure 1. Shown are the percentage changes in serum urea nitrogen concentration between the 0-s immediate postdialysis sample and the 20-s slow-flow postdialysis sample (left), between the 0-s postdialysis sample and the equilibrated postdialysis blood urea nitrogen (BUN; middle), and between the 20-s postdialysis sample and the equilibrated postdialysis BUN (right). The equilibrated postdialysis BUN were computed on the basis of the three-BUN curve-fit to 20-s and 30-min postdialysis samples. Results are presented separately for arteriovenous (AV) accesses (top) and venous catheters (bottom) dose groups.

eKt/V from Original Rate Equation*
vs
eKt/V from 30 Minute Post

Figure 2. Shown is the association between $eKt/V_{rate.orig}$ and $eKt/V_{30|20s}$ computed by fitting the two-pool variable volume model to the 30-min postdialysis BUN for 1245 patients at the 4-mo session with AV accesses. The dashed lines are reference grid lines indicating eKt/V deviations of ± 0.2. The median bias of $eKt/V_{rate.orig}$ in estimating $eKt/V_{30|20s}$ was -0.066 in all patients and -0.055 and -0.077 for those randomized to the standard- and high-dose groups, respectively. In all patients, the mean bias was -0.054, the Pearson correlation coefficient was 0.90, and the concordance correlation coefficient was 0.87. The median absolute deviation between the two measures was 0.080. *Slope = 0.60, intercept = -0.03, as defined on page 195; equivalent to a zero-intercept slope of about 0.53 for this range of K/V values.

intercept = -0.025 ± 0.014 ($P = 0.06$) and slope = 0.441 ± 0.031 ($P < 0.0001$). Because the intercept did not substantively improve the accuracy of the model, for increased parsimony we also fit a model with the intercept constrained to be 0, yielding a coefficient for K/V of 0.386 ± 0.006 ($P < 0.001$). With rounding, this produces the following equation, which we suggest for general use when the postdialysis blood draw is performed approximately 20 s after dialysis: $eKt/V_{rate.20s} = spKt/V - 0.39 \times (K/V)$.

Figure 3 presents the agreement of $eKt/V_{rate.20s}$ with $eKt/V_{30|20s}$ for the 1245 patients on AV accesses. The median bias of $eKt/V_{rate.20s}$ in estimating $eKt/V_{30|20s}$ was -0.001, and the magnitude of the error was <0.10 in 75.5% of the patients. However, $eKt/V_{rate.20s}$ exceeded the eKt/V based on the 30-min sample ($eKt/V_{30|20s}$) by at least 0.30 in 32 (2.6%) of patients. In most of these cases, the measured rebound between the 20-s postdialysis sample and the 30-min postdialysis sam-
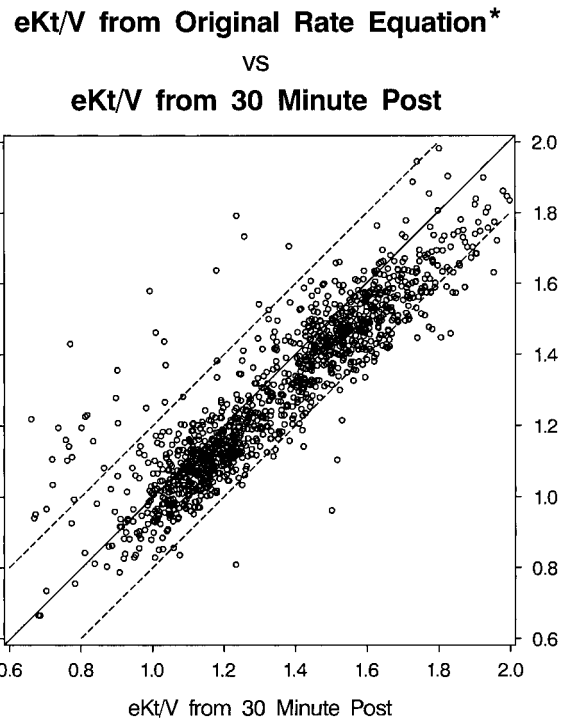
ple was too large to be compatible with the two-pool variable volume model. It is not possible to determine whether these sessions represent a true biologic phenomenon in which a small subset of sessions have much larger than expected rebound or these sessions represent errors in blood sampling or measurement. Most of these sessions remained outliers after accounting for the factors identified as significant predictors of rebound in Table 2. The robust regression method that we used minimizes the influence of outliers, so the slope coefficient of 0.39 reflects the best fitting regression to the bulk of the data, giving only limited influence to the subset with exceptionally large rebound.

For AV accesses, 18% of the total median rebound had occurred within 20 s (Figure 1). Thus, use of $eKt/V_{rate.20s}$ may underestimate rebound and consequently overestimate eKt/V if the postdialysis blood draw is obtained immediately after dialysis. For this situation, we performed similar robust regressions of $\Delta Kt/V_{0s}$ on K/V based on the immediate postdialysis sample. With an intercept included, the estimated coefficients were as follows: intercept = -0.030 ± 0.015 ($P = 0.04$) and
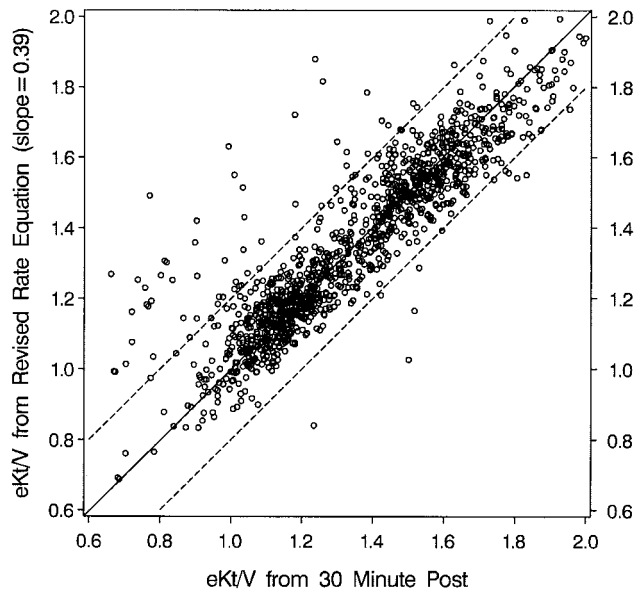
Figure 3. Shown is the association between $eKt/V_{Vrate.20s}$ estimated from the rate equation with a 0 intercept and a slope of 0.39 and $eKt/V_{30|20s}$ computed by fitting the two-pool variable volume model to the 30-min postdialysis BUN for 1245 patients at the 4-mo session with AV accesses. The dashed lines are reference grid lines indicating eKt/V deviations of ± 0.2. The median bias of $eKt/V_{rate.20s}$ in estimating $eKt/V_{30|20s}$ was -0.001 in all patients and 0.004 and -0.005 for those randomized to the standard- and high-dose groups, respectively. In all patients, the mean bias was 0.01, the Pearson correlation coefficient was 0.90, and the concordance correlation coefficient was 0.89. The median absolute deviation between the two measures was 0.052.

slope $= 0.520 \pm 0.032$ ($P < 0.0001$); with the intercept set to 0, the estimated slope was 0.458 ± 0.006 ($P < 0.0001$). Although the intercept coefficient was of borderline significance, the median absolute errors for the two models were essentially identical (0.0555 with the intercept included *versus* 0.0557 with the intercept set to 0). Hence, we suggest the 0-intercept rate equation when the postdialysis blood sample is obtained immediately after dialysis: $eKt/V_{rate.0s} = spKt/V - 0.46 \times (K/V)$.

Both of these eKt/V estimates ($eKt/V_{rate.20s}$ and $eKt/V_{rate.0s}$) use smaller adjustments for K/V than the original rate equation, $eKt/V_{rate.orig} = spKt/V - 0.60 \times (K/V) + 0.03$, although if the original equation were to be rewritten with a 0 intercept, then the magnitude of the equivalent slope would be reduced to approximately 0.53.

Rate Equation for Use in the HEMO Study

When the standard- and high-dose groups were considered separately, use of the same coefficients in both dose groups resulted in a slight bias in opposite directions in the two groups

(totaling 0.01 Kt/V units). Because these opposing biases would lead to small biases in comparisons between the dose groups of other kinetic parameters dependent on eKt/V, for the purposes of the study, it was necessary to extend the robust regression model to allow a small offset for the high-dose group. For patients on AV access, the rate equation for use in the HEMO Study based on the 20-s postdialysis BUN is $spKt/V - 0.040 \times (K/V)$ in the standard dose group and $spKt/V - 0.040 \times (K/V) + 0.01$ in the high-dose group. The median bias of this rate estimate compared with $eKt/V_{30|20s}$ was <0.001 Kt/V units in both dose groups.

Rate Equations for Venous Catheters

A smaller number ($n = 70$) of patients and sessions were analyzed to develop a rate equation for venous accesses. Here, the intercept terms did not approach statistical significance, so we report only the 0-intercept models. The optimum coefficients for the K/V terms were 0.22 ± 0.03 and 0.29 ± 0.03 for the 20-s and immediate postdialysis BUN samples, respectively.

Rebound Expressed Using a Time Constant (Tattersall Method)

The 0-intercept form of the rate equations can be re-expressed as $eKt/V_{rate} = spKt/V \times [(T - A)]/T$ (equation 1), where T denotes treatment time and A denotes the rate coefficient. For example, if A is expressed in minutes, then the 0-intercept rate equation with a coefficient of 0.39 is given by equation 1 with $A = 23.2$ min. An alternative formulation has been proposed by Tattersall (19), in which $eKt/V_{tat} = spKt/V \times [T/(T + B)]$ (equation 2).

The estimate of B in Tattersall's original description was 35 min (19). In the present data set, based on robust regression analyses, the values for B are as follows: AV accesses using 20-s postdialysis sample, 23.2 min; AV accesses using the immediate postdialysis sample, 30.7 min; venous catheters using the 20-s postdialysis sample, 13.9 min; and venous catheters using the immediate postdialysis sample, 18.5 min. There were no significant differences between the accuracy of the rate equations based on equation 1 and the corresponding Tattersall equations based on equation 2 in the HEMO Study data set.

Rebound Using Simplified Estimates of spKt/V and eKt/V

A number of previous studies have examined rebound by estimating rebound by applying the Daugirdas 2 equation (22) to the post-/pre-BUN ratio as follows: $spKt/V = -\ln(R - 0.008 \times T) + (4 - 3.5 \times R) \times (UF/Postwt)$ and $eKt/V = -\ln(Req - 0.008 \times T) + (4 - 3.5 \times Req) \times (UF/Postwt)$, where $R = C_{post(20s)}/C_{pre}$ and $Req = C_{post(30min)}/C_{pre}$, T is the session length in hours, UF is the weight loss in kg, and Postwt is the postdialysis weight in kg.

Note that this method accounts for neither continued rebound beyond 30 min nor (as T is the time from the beginning to end of dialysis) urea generation during the 30-min postdialysis period, thus making the implicit assumption that these

two effects cancel. To allow comparison with such previous studies (23–25), we used the same simplified calculations with the HEMO data. ΔKt/V = spKt/V − eKt/V was calculated by the simplified method and compared with the results of formal kinetic modeling. For AV access, using 20-s and 0-s postdialysis samples, median ΔKt/V using the simplified method was 0.213 and 0.248, respectively, somewhat higher than median ΔKt/V using the formal kinetics of this report (0.171 and 0.219, with $P < 0.001$ for simplified *versus* formal kinetics for both the 20-s and 0-s samples).

Discussion

Our results confirm previous findings (6,7) that the prime determinant of postdialysis urea rebound is the rate of dialysis, which can be expressed as K/V, or single-pool Kt/V units per hour. In addition to K/V, we found that rebound depended on whether an AV or venous access was used, consistent with the concept of CpR (3).

After controlling for K/V, type of access, and clinical center, rebound was found to be increased in men, in blacks, in patients with low predialysis systolic BP, and in patients with a large fall in systolic BP during dialysis. Rebound also was increased in patients with relatively large volumes of fluid removal during dialysis and in patients without evidence of congestive heart failure. Some of these factors are consistent with the regional blood-flow hypothesis of urea sequestration, which holds that urea may be sequestered in muscle tissues during dialysis, particularly when intradialysis blood flow to muscle is decreased, impairing washout of urea from the muscle compartment (4–6). For example, both increased cardiac output and low peripheral resistance during dialysis are associated with less postdialysis urea rebound (26). Vigorous exercise during dialysis may also reduce rebound, presumably by increasing muscle blood flow (27,28). High fluid removal rates during dialysis have been shown previously to increase postdialysis urea rebound (29). Finally, measurements of muscle tissue urea levels during dialysis support the notion of delayed washout from this compartment during dialysis (30).

In the subset with 60-min postdialysis samples, equilibrated postdialysis urea levels were not significantly different from equilibrated postdialysis urea levels projected from the 30-min postdialysis samples. This is in accordance with results of Tattersall *et al.* (19) and others, suggesting that postdialysis urea rebound is largely complete by 30 to 60 min after dialysis.

The rate equation initially used in the planning phase of the study, which was ΔKt/V = 0.6 K/V − 0.03 (6), overestimated ΔKt/V in the more extensive urea modeling sessions. On the basis of the extrapolated 30-min postdialysis BUN values, more precise rate equations were developed. The magnitude of the optimal K/V slope terms of these new rate equations depended on how the postdialysis BUN sample was drawn. For an AV access, the slope term was 0.39 when a 20-s slow-flow method was used and 0.46 when rebound was computed from blood samples drawn at the immediate end of dialysis at full blood flow.

The dependence of the coefficient of K/V on the timing of the postdialysis blood draw probably resulted from a partial equilibration of the sample obtained with the 20-s slow-flow method. With an AV access, the AV gradient begins to correct 10 to 15 s after stopping dialysis. If one waits 20 s and then does not stop the blood pump before sampling, then some rebound will have already occurred. Evidence for this was present in a comparison of the median values of BUN for the immediate postdialysis and 20-s slow-flow post samples. These should have been very similar because access recirculation is believed to occur in a very small proportion of dialysis sessions delivered through an AV access. However, the median BUN value of the 20-s slow-flow samples was substantially higher than of the immediate postdialysis samples. Conversely, the slope of 0.46 obtained with the 0-s postdialysis sample may overestimate rebound slightly as a result of the influence of undetected access recirculation. However, patients with >15% access recirculation at 1 h into dialysis were excluded, and additional exclusion of patients with an estimated recirculation of >15% at the end of dialysis reduced the estimated slope to only 0.45. The 0-s and 20-s rebound slopes can be taken as upper and lower bounds of the true rebound, one including some access recirculation but no CpR and the other including a component of CpR that is designated as part of the total postdialysis rebound.

It is of interest that the median rebound at 20 s *versus* 0 s was non-zero in the venous accesses. This suggests that perhaps a low degree of access recirculation is prevalent with venous catheters. Alternatively, it is conceivable that there may be some arterialization (in terms of urea concentration) of venous blood in the inlet bloodline; depending on catheter placement, the majority of this blood may come from the superior vena cava; superior vena cava blood is returning mostly from the high-perfusion, low-urea content zone, namely the head, and so may have a lower urea concentration than inferior vena cava blood draining the lower extremities.

The slopes for K/V reported here were based on a robust regression technique, which minimizes the influence of outliers to give a better fit to the bulk of the data. The most extreme outliers occurred for a subset of 32 (2.6%) patients with an exceptionally large rebound that was often incompatible with the two-pool variable volume model. Because the robust regression de-emphasized these data, the slope coefficients that we report are 0.03 to 0.05 h^{-1} lower than given by standard regression analysis, which is heavily influenced by outliers (data not shown). A second intensive kinetic modeling study was held at 3 yr in nine of the 32 patients with the extreme rebound. The $eKt/V_{rate.20s}$ exceeded $eKt/V_{30|20s}$ by >0.10 Kt/V units in only one of these nine patients. A similar nonreproducibility of extreme rebound in the same patients over shorter time intervals was seen in the HEMO pilot study (7), suggesting that sessions with extreme rebound may often represent measurement error or transitory phenomena.

At kinetic modeling sessions of the HEMO pilot study (7), the postdialysis blood samples were obtained 10 s, rather than 20 s, after stopping dialysis. In the pilot study data set, the estimated slope coefficients for K/V in models assuming 0 intercepts were 0.50 using standard regression and 0.45 using the robust regression technique of this article. The slope of 0.45

based on robust regression in the pilot study is similar to the slope of 0.46 for the 0-s postdialysis sample in the full-scale study. Ten seconds may be a better slow-flow period if one wants to sample before any early rebound as a result of CpR.

Because urea kinetic modeling calculations are complex, some authors have used simplified (Daugirdas 2) equations applied to the postdialysis BUN and 30-min postdialysis BUN to estimate spKt/V and eKt/V, respectively. Some reports using this simplified method have indicated relative good agreement with the original rate equation (23–25). Our data suggest that the simplified calculation overestimates rebound slightly (probably most of this is due to underestimation of the effect of urea generation, which becomes progressively more important at low postdialysis BUN values), as does the rate equation, possibly explaining the enhanced agreement between the simplified method and the original rate equation in some studies.

In summary, our findings suggest that the rate of dialysis and type of access are the prime determinants of the amount of postdialysis urea rebound. When postdialysis blood samples are drawn after a 20-s slow-flow delay, rebound can be predicted using a rate equation with 0 intercept and a slope of approximately 0.39 for AV access and 0.22 for a venous access. These slope terms account for only part of the total rebound and do not include early rebound, which may occur during the 20-s plus sampling period. If blood sampling is done when the slow-flow period is shorter, *e.g.*, 10 s, or nonexistent, then slope coefficients of 0.46 and 0.29 for AV and venous accesses would be more appropriate to use.

Our data also suggest that several patient and treatment factors affect postdialysis urea rebound, including demographic (race and age), disease-related (diabetic status), and hemodynamic (BP and fluid removal) factors. Some of these are consistent with a regional blood-flow model of urea kinetics, although other reasons for the association of these factors with postdialysis urea rebound cannot be excluded.

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