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The online measurement of hemodialysis dose (Kt): Clinical outcome as a function of body surface area

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The online measurement of hemodialysis dose (Kt): Clinical outcome as a function of body surface area.

Background. Recent advances enable the direct measurement of small molecule clearance, Kecn, during each dialysis. Average Kecn and treatment length, t, are multiplied giving total clearance, Kt. The body surface area (BSA) is a fixed transformation of height and weight and is a well recognized measure of body size. This project was conceived to search for clinical outcome-based functions for measured Kt in terms of BSA to enable simple Kt prescription guidelines for clinicians who are able to measure Kecn, and to provide foundations for future clinical research.

Methods. The data came from Fresenius Medical Care (NA) files and included more than 32,000 patients with height, weight, and paired Kecn and t measurements during December 2002. Measurements were averaged for the month and used as predictor measures in Cox models of survival time during 2003. Candidate Kt values from 30 L/treatment through 70 were examined to determine the best statistical fit for quintile and decile delimited BSA groups evaluating the best fit Kt treatment target for each group. Functional forms representing the relationship between target Kt values and mean BSA of the groups were then evaluated to determine the best fit.

Results. Kt targets increased with BSA in a curvilinear way such that the rate of increase is greater at low BSA than high. The best statistical fit was a double reciprocal form, $Kt = 1/(a + b/BSA)$; "a" and "b" are statistically derived coefficients. The form has an appealing mathematical property; Kt approaches 0 as BSA approaches 0. Other forms fit the data nearly as well, however, and can be used to estimate Kt targets for patients with different BSA.

Conclusion. Empirical, outcome-based functions of measured Kt in terms of BSA exist and can be used as aids for prescribing and judging hemodialysis treatment.

Current methods for judging hemodialysis dose evolved from mathematical models of urea kinetics [1]. The solution to those equations gives rise to a treatment ratio [2], Kt/V, values for which are commonly used as therapeutic targets [3, 4]. Total dose per treatment (Kt) is the product of dialyzer small molecule (urea) clearance (K_u) and the length of the treatment (time: t) that is divided by an estimate of the urea distribution volume in the body (V_u) yielding the ratio. K_u and V_u are not measured directly in this system. Rather, K_u is typically estimated from membrane properties (the overall mass transfer coefficient and membrane surface area, KoA) and dialysis operating parameters (blood flow rate and dialysate flow rate), then used with known values for t, blood urea nitrogen (BUN) values, and body weights before and after a dialysis treatment, and the dialysis schedule in a mathematical system that solves in iterative fashion for the unknown value of V_u. A Kt/V value can then be estimated from the results of those calculations [5].

Algebraic approximations have been developed as alternative tools to estimate a Kt/V and require knowledge of only t, fractional body weight change during treatment, and the BUN concentrations [4, 6, 7]. Iterative and algebraic methods are sometimes combined to estimate a Kt/V [8, 9]. A simple quantity comparable to the Kt/V and also calculated from BUN concentrations, the urea reduction ratio (URR), is also used to evaluate treatment [10, 11]. Those methods are part of accepted guidelines for judging dialysis treatment [4] and have contributed to better understanding of dialysis therapy over the years that may have led in turn to lower mortality among patients [12]. All methods, however, are based on BUN measurements and are not direct measurements of K_u, t, or V_u. All except the URR require substantial calculation. As such, the frequency of estimating dialysis dose has generally been limited to once monthly.

The urea kinetic methods were born and evolved during a period of time when the convenient measurement of small molecule dialyzer clearance during treatment was impractical or impossible. All contemplate a value for V_u but a number of methods are available for estimating V_u. All anthropometric methods [13, 14, 15] use height and weight as primary inputs but the exact numerical value depends on the equation used. Several urea kinetic-based methods are also available including estimates of 1 and 2 pool volumes [16]. Thus, a number of possible V values are available for a patient at any particular time depending on the method use for its estimation. Furthermore, the properties of V_u have recently come to question. Once

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thought to simply equal total body water (TBW or V), V_u now appears to be less than V in patients with chronic renal failure [17] but larger than V in patients with acute renal failure [9, 18].

Finally, the theoretical foundation on which the urea kinetic equations are based has been recently questioned when they are used to evaluate a clinical outcome, like patient survival, instead of BUN concentrations, for which they were originally designed [19]. The equations presume that the biological properties of V are limited to those of a diluent for urea. V, however, is a proxy for body mass that is associated with survival in dialysis patients [19]. Thus, the true biological nature of V_u is ambiguous and using a V as a proxy for "measured" body size by which to evaluate measured Kt is uncertain. The value for BSA, on the other hand, is fixed and certain, given weight and height, for any patient on any given day. We therefore chose it as the most reliable body size measure by which to evaluate measured Kt in these studies.

Recent technical advances permit direct measurement of small molecule clearance, called an effective on-line conductivity (or ionic) clearance (Kecn), during the course of each treatment [20–23]. The average Kecn is multiplied by t at the end of treatment to give a measured Kt. Therapeutic-dosing schedules and physiologic functions are often indexed to body size as weight or body surface area (BSA) in clinical medicine. The purpose of this project, then, was to see if clinical outcome (death hazard) based empirical functions of measured Kt could be mapped on BSA (f: Kt→BSA) to facilitate the monitoring and prescription of treatment in centers able to perform Kecn measurement and further to identify possible forms of such functions for future research.

METHODS

The technology supporting online clearance (OLC) measurements is incorporated in the 2008H and 2008K dialysis hardware systems manufactured by the Medical Products Division of Fresenius Medical Care (NA), Lexington, MA, USA. The measurement method is well reviewed elsewhere [24]. Measurements of Kecn, t, height, and body weight collected during December 2002 were extracted from the FMC (NA) data files for those 33,328 patients with at least 1 Kecn and paired t measurement. Kecn was multiplied by t to give measured Kt for each treatment. BSA (m^2) was calculated from body weight (kg) and height (cm) according to the DuBois and DuBois equation [25]

$$\text{BSA} = \text{Weight}^{0.425} \times \text{Height}^{0.725} \times 0.007184$$

Values for Kt and BSA were averaged and used as death risk predictor measures for patients treated 3 times weekly. Complete data were available for 32,763 patients, who are the subject of this report. Survival time was measured for the calendar year 2003 and evaluated by the Cox method. The analytical strategies have been described before [26, 27].

The primary analysis proceeded in 2 parts. The purpose of the first was to explore general relationships among treatment parameters, body size, and death risk in a preliminary way. The purpose of the second was to evaluate the possibility of constructing a Kt adequacy target function of BSA, f: Kt→BSA, embodied as an empirical formula that might be used clinically to estimate different outcome based Kt targets for persons with different BSA. As a supplementary analysis, we also compared the findings evolving from these data with similar analyses of older data that estimated Kt from BUN measurements [26]. Finally, we evaluated current clinical practice in terms of 1 f: Kt→BSA resulting from our evaluation of these data.

Exploratory analyses

The statistical distributions of relevant measures in the patient population and certain associations among them were evaluated in preliminary fashion using standard methods. Death risk profiles were constructed for BSA and Kt before and after certain statistical adjustments as we have done before [26, 27] to explore visually the general forms of the relationship between death risk and those measures. We also constructed similar profiles for patients grouped by BSA quintile. Such exploratory analyses are necessary prerequisites for the use of spline functions to see whether or not flex points in curves can be evaluated. The use of such techniques is futile, after all, if the relationship between 2 quantities is strictly linear or if there is no relationship at all.

Estimating Kt targets by BSA

Flex points in the death hazard by Kt risk profiles were estimated for BSA quintiles and deciles by a spline function analysis that has been described before [28, 29]. The analyses assumed 2-segment functions in which death hazard decreases with increasing Kt until it reaches a flex point, threshold, target, or knot, after which the curve tends to flatten. The goodness of fit to Cox models was evaluated in Kt increments of 1.0 L/treatment from 30 L/treatment to 70 using the conditional transformation,

$$(\text{Kt} - \text{x})_+ = \begin{cases} 0, & \text{Kt} \geq \text{x} \\ \text{Kt} - \text{x}, & \text{Kt} < \text{x} \end{cases}$$

Kt is the Kt value at which each patient was treated; x is a candidate Kt target; the "+" subscript indicates that the term is truncated. The transformation creates a deviate from the candidate, x, for each patient such that the value of $(\text{Kt—x})_+$ equals 0 for values at and above x and equals (Kt—x) for values below x. The distributions

of values in the population (e.g., the mean and standard deviation) do not effect this transformation. The values of (Kt—x) are either the difference between the patient and candidate values or 0 as specified by the equation so is independent of the mean of the values. A Cox model was performed for each candidate Kt target (70–30 + 1 = 41 models) for each BSA group and the candidate associated with the highest chi-square statistic (i.e., the best fit) was selected as the target for that group. The chi-square statistic functions here to indicate a goodness of fit between survival time and a measure of interest like age, race, or the candidate thresholds, much as the R^2 statistic reflects goodness of fit in ordinary least squares regression. Higher values indicate better fit. The chi-square curves for all BSA groups except the fourth decile group showed statistically significant values, suggesting a single maximum value that was preceded by a monotonic increase before and a monotonic decrease after the peak and were used for these analyses. See Figure 3 for examples.

Least squares regression analyses of Kt target by the mean BSA of each BSA group were performed to evaluate possible associations of the target with BSA. Several mathematical forms were evaluated to see which if any suggested a best fit. The forms were linear ($Y = a + bX$, where "Y" means the Kt target; "X" means BSA; "a" and "b" are statistically derived coefficients), exponential ($Y = \exp[a + bX]$), reciprocal of BSA ($Y = a + b/X$), reciprocal of Kt ($Y = 1/[a + bX]$), double reciprocal ($Y = 1/[a + b/X]$), multiplicative ($Y = aX^b$), square root of BSA ($Y = a + b[X^{1/2}]$), square root of Kt ($Y = [a + bX]^{1/2}$), S-curve ($Y = \exp[a + b/X]$), and quadratic ($Y = a + b_1X + b_2X^2$). The idea was to identify the general forms of possible relationships between Kt target and BSA, to identify the best statistical fit among the forms, and to recommend an easily understood general form to assist the prescription of dialysis treatment.

Supplementary analyses

An earlier study that estimated Kt from BUN measurements, instead of direct OLC measurement, found that smaller persons required proportionately greater Kt for their body sizes than larger patients [26]. Follow-up analyses of those data evaluated Kt targets by quintiles of both V and BSA using methods similar to those described above. That exercise led to a preliminary linear rule of thumb formula ($Kt = 30 + {}^1/_2V$). The rule was used to illustrate the way in which smaller persons may require greater Kt per liter of V than larger persons (Lowrie EG: *Kidney Int* 63:1962, 2003) and to assist possible interpretation of a clinical trial (Lowrie EG, et al. *Kidney Int* 66:1291, 2004). We reevaluated those data examining different mathematical forms for f: Kt→V and f: Kt→BSA to determine the extent, if any, to which they are comparable to the primary findings reported here.

Comparing an f: Kt→BSA with current clinical practice

The target Kt was estimated for selected patient groups using a representative f: Kt→BSA and compared to the Kt actually received. A similar comparison is made for males and females treated in a large national trial (the HEMO study) using published information [30].

RESULTS

We will first describe the preliminary explorations including a description of the patient population and death risk profiles observed among them. We then estimate Kt targets as functions of BSA. Those primary findings are then supplemented by comparing them to information derived from our earlier studies [26]. Finally, we evaluate current clinical practice in terms of one of the ways identified to describe f: Kt→BSA.

Preliminary analyses

Table 1 describes the distributions of relevant parameters in this patient population. The average dialysis time was about 3.6 hours (interquartile range 3.4 to 4.0 h). The average Kt was 50.7 L/treatment (interquartile range 43.7 to 57.5). Eighty percent of patients were treated between 37.7 L/treatment and 63.8. Slightly more than one half of patients were male and slightly less than one half were white. Forty-six percent (46%) were diabetic. The mean BSA was 1.85 m^2 and 98% of patients had BSA between 1.33 m^2 and 2.53.

All treatment measures (Kecn, t, and Kt) were directly correlated with all measures of body size (height, weight, and BSA). The association of measured Kt with BSA was significant [$R^2 = 0.258$, $P < 0.01$; Kt = 12.0 (±0.4 SE) + 21.0 (± 0.2 SE) × BSA] but the range of Kt at any given BSA was substantial. While the average Kt at the mean BSA was 50.8 L/treatment, for example, the 95% prediction limit at that BSA extended from about 33 L/treatment to 68.

Death risk by Kt and BSA. Figure 1 illustrates the risk profiles for BSA and Kt. The BSA profile (left panel) suggests continuing improvement of risk with increasing BSA and is similar to such profiles reported in the past. The profiles were similar whether or not they were adjusted statistically for age, gender, race, and diabetic status.

The Kt profiles (Fig. 1, right panel) compare the risk of death among the deciles of Kt following various statistical adjustments. They suggest improving risk with increasing Kt for all models and were similar in form appearing to plateau in the range of 50 to 60 L/treatment. The

Table 1. Distributions of measures

Measure	Mean or%	SD	Percentiles						
			99th	90th	75th	50th	25th	10th	1st
Age *years*	61.1	14.8	88.0	79.0	73.0	62.0	51.0	41.0	25.0
Gender% *male*	52.8								
Diabetes% *yes*	46.4								
Race									
% White	49.0								
% Black	43.3								
% Other	7.7								
Height *cm*	167.9	11.4	193.0	182.0	175.0	168.0	160.0	154.0	139.0
Predialysis weight *kg*	79.3	21.0	143.2	106.5	90.5	76.1	64.6	55.7	43.5
Postdialysis weight *kg*	76.3	20.4	138.8	102.8	87.2	73.1	62.0	53.4	41.5
Kecn *mL/min*	232.3	36.7	307.0	275.0	257.0	236.0	211.0	183.5	131.0
t *minutes*	219.2	27.3	286.0	244.0	240.0	215.0	205.0	180.0	156.0
Kt *L/treatment*	50.7	10.4	76.9	63.8	57.5	50.5	43.7	37.7	26.6
BSA m^2	1.85	0.25	2.53	2.18	2.01	1.83	1.67	1.54	1.33

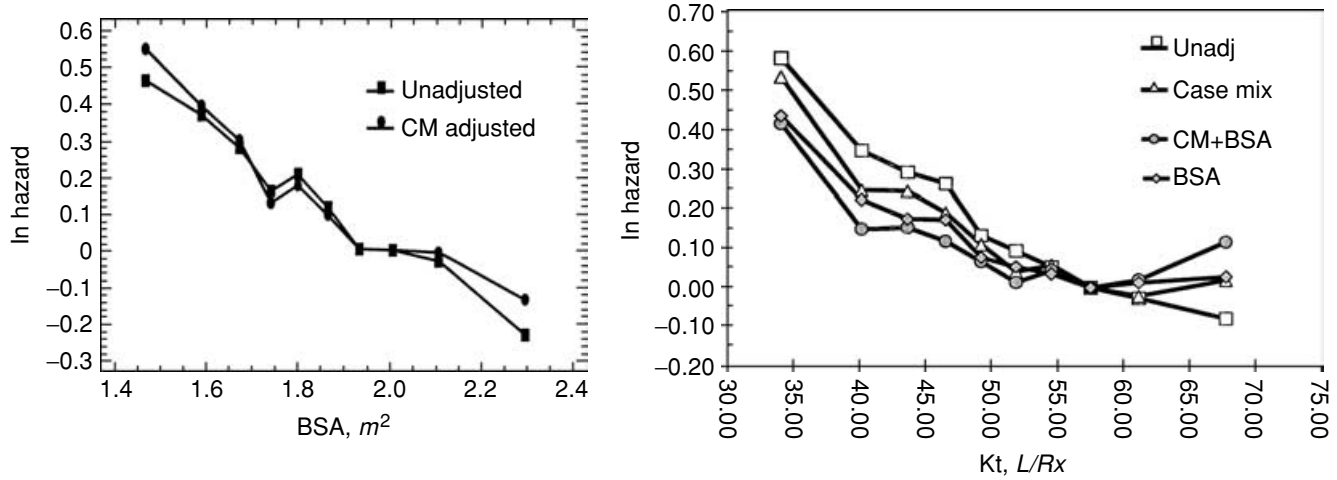

Fig. 1. Risk profiles for deciles of BSA (left panel) and Kt (right panel) with and without statistical adjustments. CM adjustment means age, gender, race, and diabetic status.

possible exception to that generality is the unadjusted profile, which may have continued to improve throughout its range. Hazard ratios for the sixth and seventh deciles and the ninth and 10th deciles were not different statistically from the eighth decile (the reference group, $P > 0.05$) for any of the 4 models shown in the figure.

Figure 2 illustrates the risk profile curves by BSA quintile. Visual review suggests that death risk tends to plateau at higher Kt in the higher BSA quintiles. The second and third quintiles appear out of sequence, however, and deciding possible targets or making therapeutic recommendations from these curves would be difficult.

Estimating Kt targets as functions of BSA

The best-fit survival models for the first, second, fourth, and fifth quintiles of BSA are shown in Figure 3. Maximum chi-square values were observed for each of the 5 quintiles (3rd quintile 55 L/treatment; curve not shown). The peaks of these curves, used to identify the maximum chi-square value, are sharper for some curves than others.

The regression analyses of Kt target on the mean of BSA for the quintiles of BSA indicated that the best fit was to a reciprocal X form ($R^2 = 0.774$, $P < 0.05$) followed by the S-curve ($R^2 = 0.772$, $P < 0.05$), double reciprocal ($R^2 = 0.767$, $P = 0.05$), log X ($R^2 = 0.740$, $P = 0.06$), and multiplicative ($R^2 = 0.734$, $P = 0.06$) forms. Figure 4 illustrates the relationship for the reciprocal X form. The linear form equation was $\text{Kt} = 18.8 + 17.3 \times \text{BSA}$ ($R^2 = 0.702$, $P = 0.08$).

The evaluation of different regression models for the deciles of BSA indicated a best fit for the double reciprocal form ($R^2 = 0.648$, $P < 0.01$) followed by the S-curve ($R^2 = 0.632$, $P = 0.01$), multiplicative ($R^2 = 0.621$, $P = 0.01$), reciprocal X ($R^2 = 0.613$, $P < 0.02$), and log X ($R^2 = 0.601$, $P < 0.02$) forms. The linear equation was $\text{Kt} = 20.7 + 16.2 \times \text{BSA}$ ($R^2 = 0.599$, $P < 0.02$). The double reciprocal form is illustrated by Figure 5.

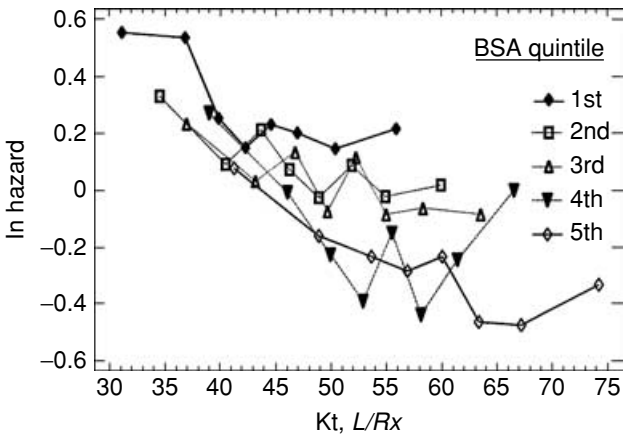

Fig. 2. Kt risk profiles for the quintiles of BSA showing log hazard (Y-axis) by the mean of the Kt octile (X-axis). These profiles were not adjusted for case mix. Case mix–adjusted profiles suggested similar relationships.

Table 2 shows statistics for the best-fit model for the quintiles, deciles, and the combination of quintiles and deciles of BSA (top portion of the table). The statistics for the double reciprocal form are also shown for the quintile analysis. Finally, statistics of several forms for the combined sample are shown in order of magnitude (left to right) of their related R^2 statistic. The table also shows the Kt target values projected by the forms as functions of BSA (bottom portion of the table).

Combining the Kt target and BSA values for the quintiles and deciles of BSA provides a more robust evaluation of the algebraic forms of fit between the measures. The best fit was to a double reciprocal form followed in order by the S-curve, reciprocal BSA, multiplicative, and log BSA forms. The linear equation was $Kt = 20.1 + 16.6 \times BSA$ ($R^2 = 0.632$, $P < 0.01$). Figure 6 illustrates the double reciprocal relationship for the combined sample.

Figure 7 compares the 5 *f*: Kt → BSA relationships for the combined sample shown in Table 2. The relationships are extrapolated beyond the limits of the observed BSA data but are constrained in a space where both measures have positive values. The presentation allows evaluation of the relationships as they approach the structural limits of clinical possibility, where Kt and/or BSA approach 0. The figure includes also the linear form of the relationship for comparison. A 0-intercept linear form, estimated from other data [30], is included to facilitate comparison with a linear form in which a 0-intercept is forced like one that is in common use today (i.e., the Kt/V).

The reciprocal X and log X curves intersect the BSA axis at 0.7 m^2 and 0.3 when Kt = 0. The linear equation intersects the Kt axis at Kt = 20.1 L/treatment when BSA = 0. The double reciprocal, S-curve, multiplicative, and linear forced 0-intercept forms approach or intersect the origin where both Kt and BSA equal 0. The S-curve approaches that origin, however, only after a substantial change of direction at low BSA. Extrapolating the curvilinear forms to high BSA suggests that the increase of Kt per increase of BSA is less at high BSA than low. Extrapolation of the linear forms to high BSA imply no such flattening so that Kt becomes quite high, particularly when the intercept is assumed to be 0.

The arrows superimposed on Figure 7 indicate the approximate first percentile (left arrow) and 99th percentile (right arrow) limits of the BSA distribution for these data. All of the curvilinear forms suggest comparable values for Kt in terms of BSA within those limits, as suggested also by Table 2.

Supplementary analysis: Comparison with earlier data

Figure 8 illustrates the best-fit double reciprocal (dark line) and the linear fit (gray line) forms for *f*: Kt→V, taken from data reported earlier [26]. The order of statistical fit for the algebraic forms was: double reciprocal ($R^2 = 0.811$, $P < 0.05$), S-curve ($R^2 = 0.803$, $P < 0.05$), reciprocal X ($R^2 = 0.794$, $P < 0.05$), multiplicative ($R^2 = 0.777$, $P < 0.05$), and log X ($R^2 = 0.772$, $P = 0.05$). The linear form fit was $R^2 = 0.737$, $P = 0.06$. The thin, dashed line illustrates Kt/V = 1.2 and is included for comparison.

These data were also evaluated in terms of BSA. The order of statistical fit was: double reciprocal ($R^2 = 0.844$, $P < 0.05$), S-curve ($R^2 = 0.834$, $P < 0.05$), reciprocal X ($R^2 = 0.823$, $P < 0.05$), multiplicative ($R^2 = 0.821$, $P < 0.05$), and log X ($R^2 = 0.812$, $P < 0.05$). The linear form fit was $R^2 = 0.793$, $P < 0.05$. The double reciprocal coefficients for "a" and "b" were 0.0119 and 0.0182, respectively. The projected Kt targets resulting from those are lower than those suggested in Table 2, particularly at high BSA. They are 33.2 L/treatment, 40.1, 47.6, 52.8, and 55.6 at BSA values of 1.0 m^2, 1.4, 2.0, 2.6, and 3.0, respectively.

Comparing *f*: Kt→BSA with current clinical practice

The mean and median target Kt calculated using the double reciprocal equation (50.6 L/treatment and 50.5) and actual Kt values (50.7 L/treatment and 50.5) were close to each other. The lower quartile, median, and upper quartile of differences (actual—target) were 5.4 L/treatment less, 0.40 more, and 6.0 more than target, respectively. Table 3 compares treated to target values for different subgroups of patients.

The mean BSA for diabetic and nondiabetic patients was 1.87 and 1.82 m^2, respectively, and the mean Kt at which they were treated was 50.8 and 50.3 L/treatment. The comparable Kt targets were 51.0 and 50.0, respectively. Female subgroups were treated at Kt slightly less than the targets implied by these data while male subgroups were treated at slightly higher Kt.

Information taken from the HEMO study [30] is included in the table for comparison. Females in the

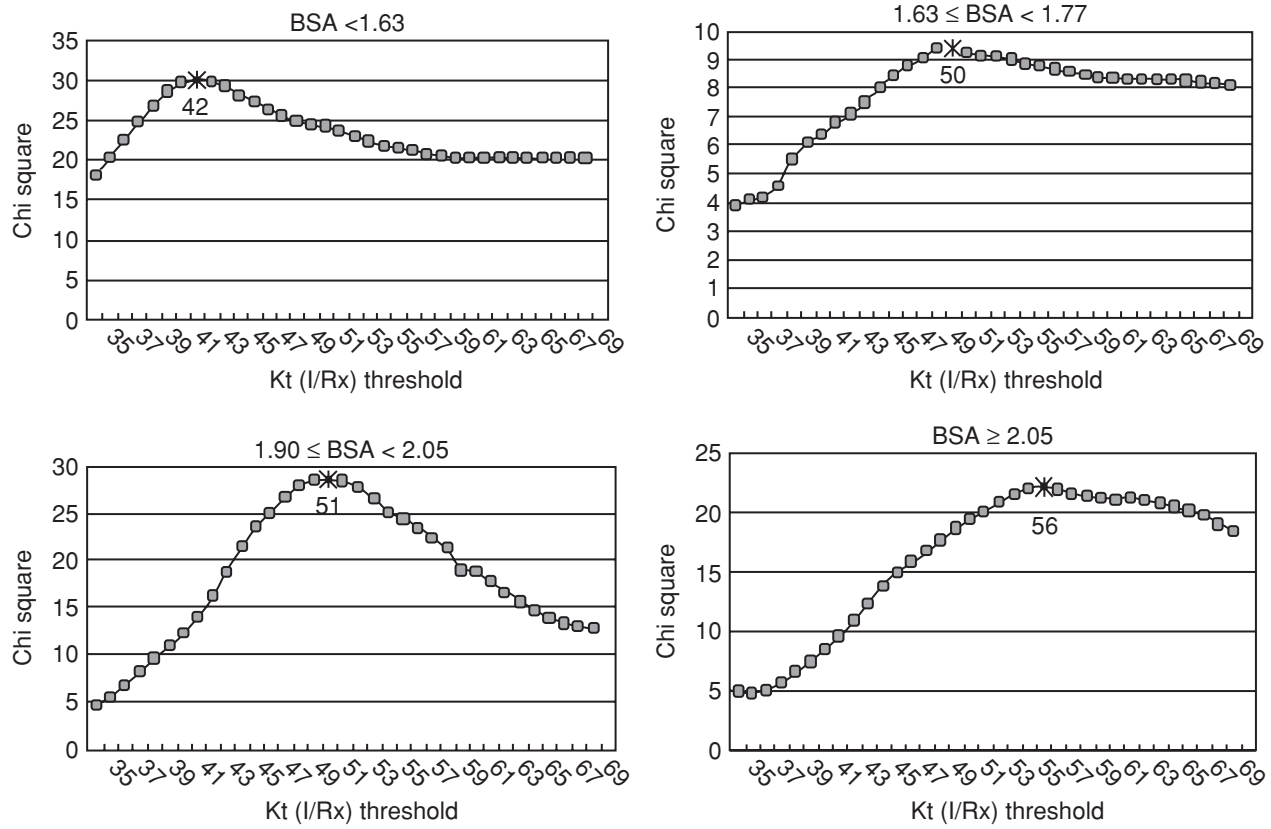

Fig. 3. Death hazard fit curves by Kt target for the 1st, 2nd, 4th, and 5th quintiles of BSA. The best-fit target for the first through fifth quintiles were 42 L/treatment, 50, 55 (curve not shown), 51, and 56, respectively.

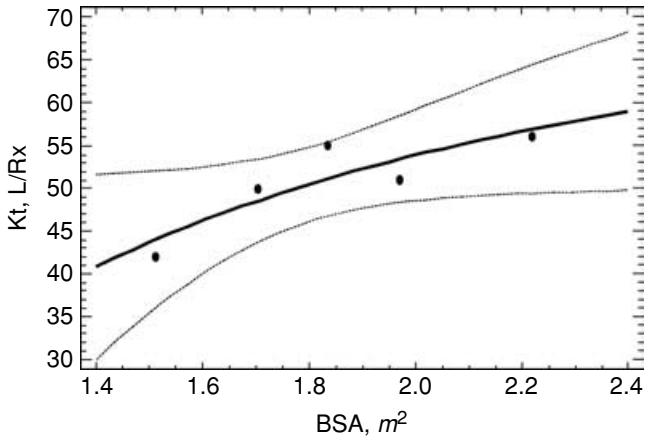

Fig. 4. The best-fit (reciprocal X) to Kt target for each BSA quintile by the mean of BSA for that quintile. The dark solid line is the best-fit relationship. The dashed lines indicate the 95% confidence interval for the regression. The standard error of estimates was 3.0 L/treatment, that is, 5.9% of the mean Kt at the mean BSA. See Table 2 for other regression statistics.

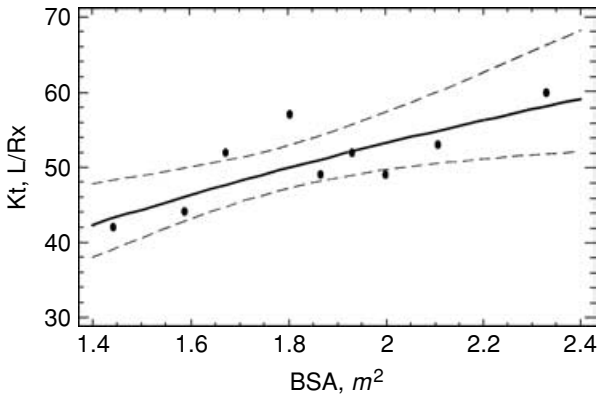

Fig. 5. The best-fit (reciprocal X) to Kt target for each BSA decile by the mean of BSA for that decile. The dark solid line is the best-fit relationship. The dashed lines indicate the 95% confidence interval for the regression. The standard error of estimates was 3.7 L/treatment, that is, 7.3% of the mean Kt at the mean BSA. See Table 2 for other regression statistics.

standard treatment group were treated at Kt nearly 10 L/treatment lower than target (21%). Males were treated at 5.2 L/treatment less. Patients in the high-dose groups were treated at higher Kt than these targets.

DISCUSSION

Technologic advances now enable measurement of small molecule clearance, Kecn, during the course of each hemodialysis treatment [24]. Thus, the total clearance received during each treatment, Kt, can be measured

Table 2. Comparison of the algebraic forms regression statistics and projections from equations

Data model	Quintiles 1/BSA	Quintiles 1/1/BSA	Deciles 1/1/BSA	Combined 1/1/BSA	Combined S-curve	Combined 1/BSA	Combined Multip	Combined lnBSA
R^2%	77.4	76.7	64.8	68.6	67.6	66.2	65.7	64.9
P value	<0.05	0.05	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
Coefficient b[a]	−61.0	0.0260	0.0225	0.0237	−1.15	−56.8	34.6	31.0
Coefficient a[a]	84.4	0.0055	0.0075	0.0069	4.56	82.0	0.63	32.0
BSA m^2	Values of Kt *L/treatment*							
1.0	23.4	31.6	33.3	32.7	30.0	25.2	34.5	32.0
1.2	33.5	36.7	38.0	37.6	36.4	34.7	37.7	37.6
1.4	40.8	41.4	42.3	42.0	41.8	41.5	42.6	42.4
1.6	46.2	45.8	46.3	46.1	46.3	46.5	46.3	46.5
1.8	50.5	49.9	49.9	49.9	50.2	50.5	49.9	50.2
2.0	53.9	53.8	53.2	53.4	53.5	53.6	53.5	53.5
2.2	56.6	57.5	56.3	56.7	56.4	56.2	56.6	56.4
2.4	58.9	60.9	59.1	59.7	58.9	58.4	59.8	59.1
2.6	60.9	64.2	61.7	62.5	61.1	60.2	62.9	61.6
2.8	62.6	64.7	64.2	65.2	63.9	61.7	65.9	63.9
3.0	64.0	70.2	66.5	67.7	64.9	63.1	68.8	66.0

The dashed lines bracketing BSA 1.4 through 2.4 are the approximate 98% distribution interval for BSA. Values outside of the dashed lines are extrapolations beyond those data limits to allow comparison of the estimates. Reciprocal BSA (1/BSA): Y = a + b/X; double reciprocal (1/1/BSA): Y = 1/(a + b/X); S-curve (S-curve): Y = exp(a + b/X); multiplicative (multip): Y = aX^b; log of BSA (ln BSA): Y = a + b(ln X)

[a]The coefficients "a" and "b" are coefficients in the 4 equations.

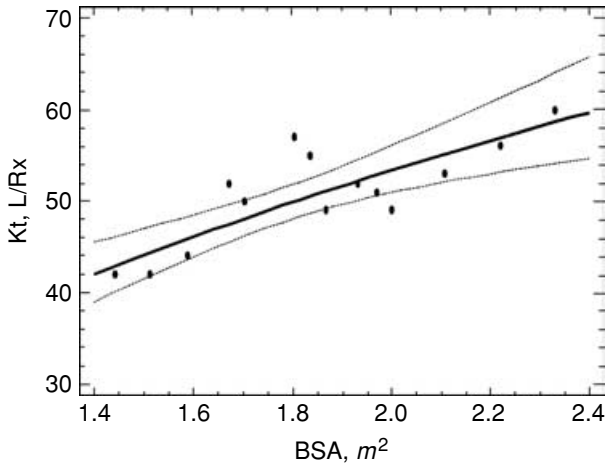

Fig. 6. The best-fit (double reciprocal) to Kt target for each BSA quintile and decile by the mean of BSA for that quintile or decile. The dark solid line is the best-fit relationship. The inner dashed lines indicate the 95% confidence interval for the regression. The standard error of estimates was 3.2 L/treatment, that is, 6.3% of the mean Kt at the mean BSA. See Table 2 for other regression statistics.

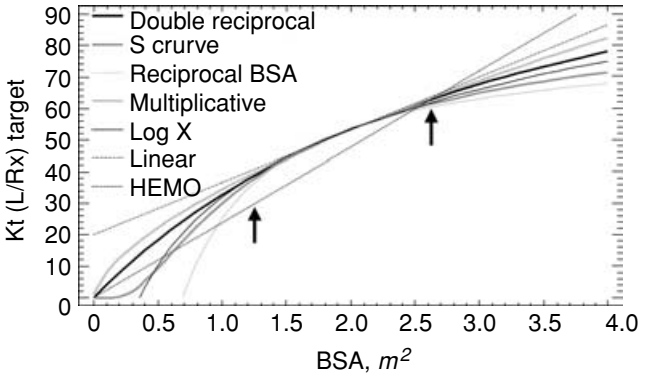

Fig. 7. Comparison of extrapolated curves for the double reciprocal (thick, black curve), S-curve (thick, dark gray curve), reciprocal X (thin, gray curve), multiplicative (thick, light gray curve), and log X (thin, black curve) forms. The linear form for these data is also shown (thin, dash—dot—dash line). A linear, 0-intercept form taken from a regression of the mean BSA and mean Kt for males and females in the standard treatment arm of the HEMO study [30] through the 0,0 origin is provided for comparison (thin, dashed line). The vertical arrows indicate the approximate 98% distribution interval of BSA.

directly. Two companies (Fresenius Medical Care, AG, Bad Homburg, Germany and Lexington, MA, USA; Gambro, AB, Stockholm, Sweden and Lakewood, CO, USA) offer the capability, and other technologies have been proposed [31] to support the goal. The body surface area of patients is an unambiguous transformation of measured height and weight [25] that is commonly used to evaluate physiologic functions [32]. This study was conceived and executed to see if empirical, clinical outcome-based functions of Kt in terms of BSA could be identified.

The studies suggest that higher total dialysis dose per treatment, Kt, is required for persons of large body size than small. The finding is not surprising, but to the best of our knowledge has not been demonstrated before using independent estimates of dose and size.

The mathematical forms of the empirical best fit relationships identified here appear curvilinear, bowing upward such that the increase of "necessary" Kt increases with BSA more rapidly at low BSA than high. Thus, the target Kt/BSA is higher for small than large persons. For example, the Kt projected for persons with BSA = 1.0 m^2, 2.0, and 3.0 from the double reciprocal form are 32.7 L/treatment, 53.4, and 67.7, giving Kt/BSA = 32.7 L/m^2, 26.7, and 22.6, respectively. Similarly, Figure 8 suggests that the target Kt at V = 25 L, 40, and 55 are

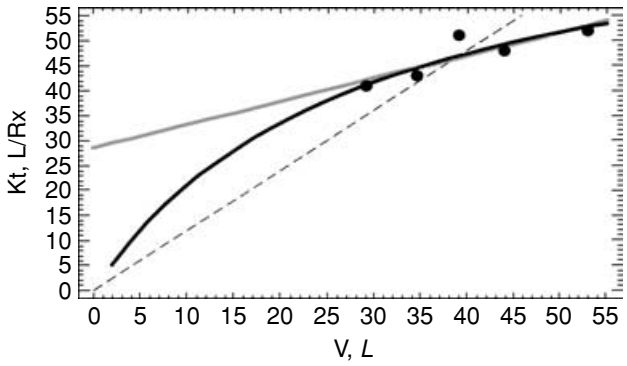

Fig. 8. The double reciprocal best-fit (black curve: $R^2 = 0.811$, $P < 0.04$) and linear (gray line: $R^2 = 0.737$, $P = 0.06$; Kt = 28.6 + [0.46 × BSA]) relationships for Kt target by volume of distribution (V) taken from data reported earlier [26]. A 0-intercept, linear relationship Kt = 0 + [1.2 × V] is shown for comparison (dashed line).

38 L, 48, and 53, corresponding to Kt/V values of 1.52, 1.20, and 0.96, respectively. These findings are entirely consistent with earlier observations, suggesting that smaller patients require proportionately greater Kt for their body sizes than larger patients [26, 27].

The most appealing mathematical form considered here is the double reciprocal construct, for at least 2 reasons. First, 4 of the 5 analytical sets (quintiles, deciles, combined, supplementary V, and supplementary BSA) evaluated here fit that construct best. Second, the form approaches the 0,0 origin when BSA is extrapolated to very low values.

It is clinically reasonable to presume that 0 total clearance should be required at BSA = 0. HEMO study investigators opined similarly. Females treated in the standard therapy arm of their study [30] experienced marginally worse survival than males, and they suggested that the difference could be explained physiologically by a nonlinear relationship with a 0 intercept such as a "power function" (Depner T, et al. *Kidney Int* 66:1292, 2004). The reciprocal BSA and log BSA forms reported here suggest that a negative Kt is needed when extrapolated to low BSA. The linear form suggests that about 20 L/treatment would be required when BSA = 0—a form to which the HEMO investigators appropriately objected. The double reciprocal construct is a nonlinear form in which the Kt target approaches 0 in a smooth and continuous way as BSA approaches 0, as the investigators suggested. That is a mathematical property of $Y = 1/(a + b/X)$ because $(a + b/X)$ approaches infinity as X approaches 0 and $1/(a + b/X)$ approaches 0 as $(a + b/X)$ approaches infinity.

The HEMO study investigators based their opinion in part on a universal scaling law that relates physiologic functions across mammalian species to a power function of body mass [33, 34]. That power function is the same as our multiplicative model, $Y = aX^b$ [34]. Four of our 5 analyses suggested a significant multiplicative relationship between Kt target and BSA, and the fit was nearly significant for the fifth, even though it was not the best-fit relationship for any. The multiplicative form, like the double reciprocal form, is curvilinear and forces the relationship to the 0,0 origin because 0^b equals zero. The universal scaling law contemplates an increase of glomerular filtration rate proportional to body mass raised to the $^3/_4$ power. Our quintile, decile, and combined sample analyses implied that the powers to which BSA was raised to achieve target Kt values were 0.67, 0.60, and 0.63, respectively. As such, these findings may find theoretical foundation in current physiologic concepts about the cross species scaling of physiologic functions [34].

Requiring a linear equation with a zero intercept for *f*: Kt→BSA, similar to the conventional Kt/V construct for example, leads to undertreatment for small patients or to very high treatment recommendations for large patients, depending on the slope for the equation. All of the curvilinear forms illustrated here give comparable estimates of Kt target values within the range of BSA studied here, however, theory not withstanding. As such, any of them can be used for clinical purposes provided that the patient's BSA is in or near that range.

The mathematical forms of *f*: Kt→BSA identified from direct measurement of Kt and our approximation of it from BUN measurements were similar but the target Kt projected from them were different. The BUN-based targets were lower than the measured targets, particularly at high BSA. There are several possible reasons for the apparent discrepancy.

First, the Kt estimates from the 2 studies might not be comparable because earlier studies based on pre and post dialysis BUN measurements could reflect an effective Kt, $K_e t$, while the OLC measurements could reflect a higher, dialyzer Kt, $K_d t$. A $K_e t$ might be lower than a $K_d t$ due to the recirculation of freshly dialyzed blood through the dialyzer, for example. Reports, however, have suggested that Kecn is often less than the K_d for urea and the matter has been recently discussed in substantial detail [24]. Kecn reflects the effective clearance of urea from the blood and not the dialyzer clearance of urea even over a wide range of recirculation fractions to include the purposeful reversal of the arterial and venous bloodlines [24]. The important point here is that Kecn reflects an effective small molecule clearance that is actually delivered to a patient more than it does a dialyzer clearance that one might determine from evaluations of dialyzer performance or from manufacturers' specifications.

Our earlier investigations [26] were taken from measurements of predialysis and postdialysis BUN concentrations and, thus, were also patient and not dialyzer oriented. As such, they are comparable to the OLC measurements. It is therefore unlikely that the difference

Table 3. Clinical practice and the Kt target

Gender	Race	Current practice		Analysis	Difference[b]	
		BSA	Kt	Kt target	L/Rx	%
This study[a]						
Patients	All	1.85	50.6	50.5	0.1	0.12
Gender	Males	1.94	53.9	52.2	1.7	3.24
	Females	1.74	47.0	48.7	−1.7	−3.32
Race	Black	1.88	51.7	51.1	0.6	1.14
	White	1.84	50.0	50.4	−0.4	−0.69
	Other	1.73	48.1	48.4	−0.3	−0.30
Diabetes	Yes	1.82	50.8	51.0	−0.2	−0.27
	No	1.87	50.3	50.0	0.3	0.58
Race by gender	Black males	1.97	55.6	52.9	2.7	5.39
	Black females	1.79	48.1	49.5	−1.4	−2.75
	White males	1.93	53.1	52.1	1.0	1.93
	White females	1.72	46.3	48.2	−1.9	−3.91
	Other males	1.82	50.8	50.1	0.7	1.72
	Other females	1.62	45.0	46.4	−1.4	−2.67
HEMO study[a]						
Standard dose	Males	1.83	45.5	50.7	−5.2	−10.26
	Females	1.68	38.2	48.1	−9.9	−20.58
High dose	Males	1.83	59.6	50.7	8.9	17.55
	Females	1.68	51.7	48.1	3.6	7.48

[a] The Study statistics for both current practice and Kt targets are the means taken over all patients in each patient group. The HEMO statistics were taken from the literature [30]. The Kt targets were calculated from the mean BSA for that HEMO study group.
[b] Kt—Kt target and 100 × (Kt—Kt target)/Kt target, respectively. L/Rx means L/treatment.

between Kt targets resulting from these and the earlier studies evolved from the measurement of a K_d in one case and a K_e in the other.

Second, the apparent discrepancy between the Kt target projections from our OLC and BUN data sets might involve our choice of the estimate for V to calculate a Kt from a Kt/V [26]. We estimated V by the Chertow method [13]; kinetic estimates of V are said to be lower than the Chertow estimates [17]. If so, our estimates of Kt targets based on BUN measurements would be too high all else equal. The explanation therefore seems unlikely since the BUN-based targets were lower.

Finally, the reference point for estimating Kt during this project was different from the earlier project [26]. This project relied on direct measurements of effective small molecule clearance at the patient-dialyzer interface, as explained above and elsewhere [24]. The BUN-based estimate [26] reflected an apparent urea clearance from 1 pool of a complex multipool volume that can be approximated using a variety of different methods. We used only 1 of those methods [26]. A root cause of the difference might be found in the different characteristics of the reference points and/or the data sets. In any event, the curvilinear form of the death hazard–based *f*: Kt→BSA was similar in both, and similar also to the *f*: Kt→V, even if the targets projected by them were somewhat different. Further, direct measurements should take preference over algebraic approximations. Finally, our goal here was to evaluate outcome-based *f*: Kt→BSA using OLC-derived information, not BUN measurement–derived estimates.

The *f*: Kt→BSA strategies for prescribing and judging treatment are easily implemented in the clinical setting for those facilities supporting the on-line measurement of small molecule clearance. The BSA is easily calculated. The target Kt can then be chosen from a table like that illustrated in the Appendix. Values that are equivalent for practical purpose also can be calculated from the log X equation form, $Kt = 32 + 31(\ln BSA)$. Achievement of the target Kt then can be monitored with each and every treatment by OLC.

Implementation strategies are somewhat more difficult for clinicians who cannot measure Kecn. A target Kt can be selected from *f*: Kt→BSA, however. That Kt can be prescribed from the length of treatment and a clearance value estimated from manufacturers' specifications for the dialyzer (the KoA), blood flow rate, and dialysate flow rate. The URR resulting from such a prescription can be converted to a Kt/V by a variety of methods (e.g., $Kt/V = \ln [1–URR/100]$) that can be multiplied by an estimate of V (e.g., the Chertow V [13]), yielding a Kt, as has been done elsewhere [26], to check the prescription.

The Kt at which these patients were treated was on average close to the target value calculated for them. Clinicians tend to prescribe more Kt than required by a fixed Kt/V or URR rule because higher URR and, therefore, Kt/V, is administered to small patients than to large patients [35]. Hence, clinical judgment appears to lead clinicians toward conclusions, suggesting that relatively more treatment is required for smaller persons than large—quite similar to these and other findings [26, 27]. Thus, the findings reported here may provide support for the role of clinical judgment in medical practice. Treatment in patient groups with higher BSA, however, tended to be at Kt values somewhat higher than target

while groups with lower BSA tended to be treated at values somewhat lower than target. Males, for example were treated at 1.7 L/treatment higher than target (3.2%) while females were treated at 1.7 L/treatment less than target (−3.3%). Even so, the differences between current practice and estimated target were relatively small on average.

We are not able to say how Kt was estimated in the HEMO study [30], but it was not by the methods used here. Thus, the Kt values are not strictly comparable. Nonetheless, it is interesting to note that females treated in the standard dose arm of the study appear to have been treated at Kt more than 20% lower than the target implied by these data. Males were treated at Kt only about 10% less than the target. The HEMO data suggested that females in the standard dose arm of the study had marginally worse survival than did the other 3 groups [30] and, thus, they may have been relatively undertreated when judged by curvilinear Kt target criteria like those implied by data like these.

These findings should be qualified in several ways. First, they are empirical—finding equations that best fit the data. As such, different data could lead to different equations. The theory supporting our choice of the double reciprocal form is appealing. The mathematical forms of our OLC-measured and BUN-estimated Kt targets were both double reciprocal, but the projections resulting from them were different. Thus, different Kt measurement techniques can lead to different target estimates for the same BSA.

Second, all statistical estimates are vulnerable to the methods used. There may be other ways to estimate the targets for our BSA and V groups. Furthermore, there is no assurance that the statistical best fit among the 41 Cox models evaluated for each group was indeed the true target. It is nonetheless interesting and reassuring that statistically ordered curvilinear relationships between Kt target and BSA could be demonstrated for all of our samples, even those with only 3 degrees of freedom—5 data pairs.

These findings should be confirmed or modified by further study. Analytical methods that permit evaluation of targets for different groups within a single survival model may become commonly available and could measurably facilitate an exercise like this.

CONCLUSION

These data suggest that there exist curvilinear outcome-based relationships between BSA and Kt. The relationships reported here can be easily implemented at no incremental cost in dialysis facilities supporting the online measurement of small molecule clearance.

APPENDIX. Minimum total treatment (Kt) targets by body surface area (BSA) double reciprocal relationship

BSA	Kt
1.20	37.6
1.22	38.0
1.24	38.5
1.26	38.9
1.28	39.4
1.30	39.8
1.32	40.3
1.34	40.7
1.36	41.2
1.38	41.6
1.40	42.0
1.42	42.4
1.44	42.9
1.46	43.3
1.48	43.7
1.50	44.1
1.52	44.5
1.54	44.9
1.56	45.3
1.58	45.7
1.60	46.1
1.62	46.5
1.64	46.9
1.66	47.3
1.68	47.7
1.70	48.0
1.72	48.4
1.74	48.8
1.76	49.2
1.78	49.5
1.80	49.9
1.82	50.3
1.84	50.6
1.86	51.0
1.88	51.3
1.90	51.7
1.92	52.0
1.94	52.4
1.96	52.7
1.98	53.1
2.00	53.4
2.02	53.7
2.04	54.1
2.06	54.4
2.08	54.7
2.10	55.1
2.12	55.4
2.14	55.7
2.16	56.0
2.18	56.3
2.20	56.7
2.22	57.0
2.24	57.3
2.26	57.6
2.28	57.9
2.30	58.2
2.32	58.5
2.34	58.8
2.36	59.1
2.38	59.4
2.40	59.7
2.42	60.0
2.44	60.3
2.46	60.6
2.48	60.8
2.50	61.1

APPENDIX. Continued

BSA	Kt
2.52	61.4
2.54	61.7
2.56	62.0
2.58	62.2
2.60	62.5
2.62	62.8
2.64	63.1
2.66	63.3
2.68	63.6
2.70	63.9
2.72	64.1
2.74	64.4
2.76	64.6
2.78	64.9
2.80	65.2

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