Optimizing the Measurement of Dialysis: Which Denominator?

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Comparisons of outcomes in men versus women undergoing chronic maintenance hemodialysis have shown differences usually favoring men despite larger doses given to women (1–3). All agree that larger doses are given to women because of their smaller size, which allows delivery of more dialysis within a short time frame. When the prescribed dose is adjusted to body size, providing "equal" doses for men and women, the outcome in women is often worse, suggesting underdialysis (4). In the Hemodiaysis (HEMO) Study, increasing the dose in women appeared to improve survival and other outcomes but attempts to link the improved survival to their smaller size, measured in several ways, were unsuccessful although the investigators acknowledged that separating sex and size was difficult (5). The investigators concluded tentatively that sex in some unknown way was responsible for the improved response to the higher dose (5). Still championing the idea that size was responsible, Daugirdas *et al.* showed that substitution of surface area (SA) in place of V in the dose expression Kt/V might explain the HEMO Study findings (6). They developed a method for converting standard Kt/V to a SA normalized dose (SAN-stdKt/V), allowing continued application of currently accepted guidelines for dialysis dosing (7). After normalizing by SA, they showed that women randomized to the higher dose in the HEMO Study actually received a dose that was equal to the lower dose given to the men (see Figure 1 below) (6). To test the validity of the SA modified dose expression, Ramirez and colleagues recently reported outcomes in a larger cohort of 7229 Centers for Medicare and Medicaid Services (CMS) patients (3).

Choices for a Size-Normalizing Denominator

Concentration-dependent toxicity is central to our current understanding of uremia, a concept verified by the success of dialysis. Although changes in the volume of toxin distribution affect concentrations acutely, volume has little to do with steady state concentrations (C). In a simple single pool model, C is directly proportional to generation (G) and inversely proportional to clearance (K): C = G/K. We assume that G varies with patient size, so K must be matched to the patient's size in order to control C at an absolute subtoxic level that is common to everyone regardless of size. The fractional clearance of urea (Kt/V) is easily determined from modeling the pre/post BUN during a single hemodialysis, so the denominator (V_{urea}) is automatically included without need for further calculation. V_{urea}, a measure of body water volume, is not only convenient is also an appropriate denominator to use as a factor for patient size (and G). V was attractive from the beginning because it was considered a measure of lean body mass free of fat mass, an unlikely source of uremic toxins. However, the major component of body water in normal people is muscle mass, augmented by edema fluid in patients with CKD. For reasons that are not entirely clear, muscled individuals are less likely to die from uremia and appear to need less dialysis than their thinner counterparts, so it appears that muscle, like fat or edema fluid, is not a major source of uremic toxins. As a patient gains more body fluid either as extracellular edema or as intracellular muscle mass, Kt/V must be increased to meet the dose standard, whereas the need for more dialysis is not proportionately increased. That leaves visceral cell mass (VCM) as the most likely source of toxins and therefore the best denominator for dialysis dosing if the goal is to reduce toxin concentrations to a constant low level (8). VCM scales better to body SA than to body weight or V, similar to native kidney glomerular filtration (GFR) (8–10).

Some have questioned the use of body size as a denominator for dialyzer clearance because body size appears to be an independent predictor of patient mortality. Many studies, including HEMO and the study by Ramirez *et al.* (see their Figure 2), show that larger patients have lower mortality rates independent of dialysis dose and often attributed to better nutrition (3,11–13). When corrected for this effect, Kt/V shows an even steeper relationship to mortality (14). Ramirez *et al.* corrected for this effect using an anthropometric estimate of V (Vant) and found little influence on survival in their cohort (3). Regardless of the reason for the effect of size on outcome, any attempt to normalize the dialysis dose to body size must take into consideration this potential confounder.

Advantages of SA

Most dimensions and functions of living organisms are better sized by SA than mass (10,15). Body water

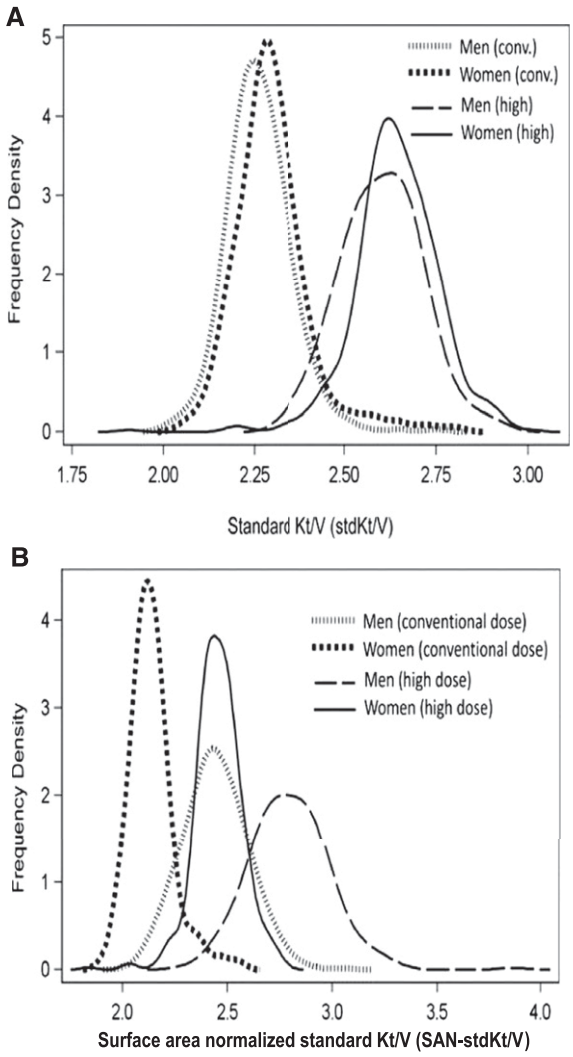

Figure 1. | Distribution of dialysis doses in the Hemodialysis (HEMO) trial (6). (A) a clear and equal separation was achieved in men and women when the dose was expressed as stdKt/V. (B) When the same doses were normalized by surface area instead of V, the higher dose in women was equal to the lower dose in men.

volume (V) is directly proportionate to body mass, whereas SA scales to the two-thirds power of mass. This means that smaller patients have a larger SA/V ratio than larger patients and attempts to size-normalize treatments according to body mass or V run the risk of underdosing these patients. When V is used instead of SA as the normalizing factor, the potential for error is even greater in women because their V/SA ratio is much lower than men due to a higher body fat content (Figure 2 below). Underdosing of hemodialysis in women and small patients in general has been suggested by several investigators (7,12,13,16,17).

SA is also more tightly associated with body height and weight than V. It is difficult to imagine a change in height or weight without a change in SA. In contrast, a gain in weight due to obesity increases Vant without an equal magnitude increase in actual V.

It is unlikely that SA is directly related to uremic toxin production; rather, its mathematical quantification from a two-thirds (0.67) power of body mass puts it closer to the three-quarters power (0.75) predicted by the universal scaling law (10).

Meaning of SAN-stdKt/V

Recommendations for use of standard Kt/V (stdKt/V) are included in the latest Kidney Disease and Outcomes Quality Initiative (KDOQI) practice recommendations but are not part of the guidelines because stdKt/V has not been tested in a controlled clinical trial, although its use is a logical extension of such studies (18). Conversion of spKt/V to standard Kt/V is an attempt to normalize the relatively inefficient intermittent clearance to a single continuous equivalent clearance expressed as a weekly dose, similar to peritoneal dialysis. The resulting new measure of dialysis allows comparisons among patients dialyzed according to different weekly schedules. StdKt/V is also used to avoid the divergence of dose and solute levels as the dose is increased beyond the plateau region. For example, doubling spKt/V from 2.0 to 4.0 during a single dialysis session has little effect on dialyzable small solute concentrations and little effect on stdKt/V. In the HEMO Study, patients in the intensive treatment group received a dose that was 32% higher than controls when measured by spKt/V but only 16% higher when measured by stdKt/V.

SAN-stdKt/V is essentially stdKt/SA normalized to stdKt/V using a population statistical mean value for Vant/SA. A Vant/SA value of 17.5 was used in the Ramirez study based on HEMO Study data. Therefore, a patient with Vant/SA equal to 17.5 would have a SAN-stdKt/V equal to stdKt/V. This transformation gives the new parameter, SAN-stdKt/V, a familiar range of values and allows use of known mortality correlations with stdKt/V.

Dose versus Outcome

The HEMO Study showed no benefit beyond a spKt/V of 1.3 (11). In the observational study by Ramirez *et al.*, the authors acknowledge that the markedly reduced hazard ratios in the spKt/V range of 1.2–1.6 in both sexes (see their Figure 3) were not expected and suggested a bias that is consistent with a dose targeting bias attributed to comorbidities that prevent patients from achieving the targeted dose (19). For example, use of central venous catheters for blood access, which are known to increase mortality, may also prevent achievement of higher doses.

Ramirez *et al.* were unable to model patient-specific values for V because they had no way to measure K in their cohort of patients with limited CMS data. As noted above, urea modeling provides the ratio K/V; thus, to obtain an accurate value for V, one needs an accurate value for K or *vice versa*. The scatter in their Figure 1 is partly due to application of an anthropometry-based estimate of V (modified Watson equation), a technique well suited to population studies but often fraught with large errors when applied to individual patients (20). Formal urea modeling using accurate values for K, based on individual blood and dialysate flow rates and dialyzer KoA should sharpen the results by providing more accurate values of V in each patient.

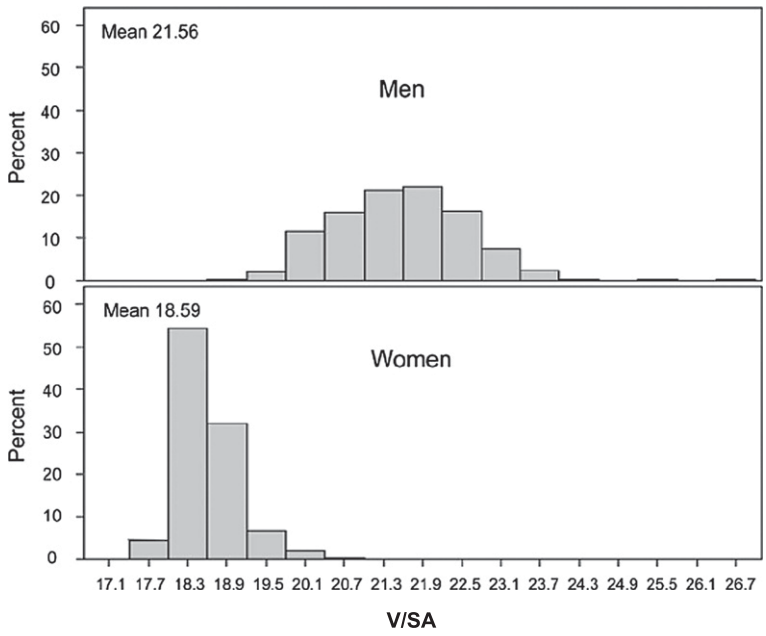

Figure 2. | Distribution of volume per unit of surface area in men compared to women enrolled in the Hemodialysis (HEMO) trial (6). The ratio of V (liters) to surface area (M^2) shows only a small overlap. V was determined by the Watson anthropometric equation (20).

Practice Recommendations

In the Ramirez study, a higher dose of dialysis was associated with improved patient survival in both women and men, consistent with other observational studies (3). It is not surprising therefore to see better survival in women when the dose versus outcome curve is shifted to the left more in women than in men. Such a shift occurs when SA is substituted for V in the clearance denominator because the surface area to V ratio is higher in women (and smaller patients) compared with men as shown in Figure 2 above. However, the improved survival in both sexes at higher doses is inconsistent with results from the HEMO randomized controlled clinical trial. A more conservative conclusion from this and other outcome studies is that women respond better to higher doses for reasons that are not clear. This was the conclusion of the HEMO Study investigators who stopped short of recommending a change in current practice, which normalizes the dose according to V (5). The bottom line is that we do not know how to normalize the dose but we suspect that use of V as a universal denominator could underdose women and small patients. The toxin generation rate is generally accepted as the best normalizing factor but there are many toxins and their generation rates may vary with diet, gut flora, stress, exercise, age, visceral organ mass, and the activity and size of other body components. Given the universal scaling law and the correlation with normal GFR, body SA is logically a better denominator than V. This reasoning supports a bias toward higher doses in women and smaller patients. Population studies such as that reported by Ramirez *et al.* are helpful for developing guidelines for the average patient, but when faced with an individual patient, clinical judgment should prevail.

Disclosures

None.

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See related article, "Dialysis Dose Scaled to Body Surface Area and Size-Adjusted, Sex-Specific Patient Mortality" on pages 1977–1987.