HEMO Revisited: Why Kt/V_{urea} Only Tells Part of the Story

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In this issue of the Journal of the American Society of Nephrology, a posthoc analysis of the data and samples of the Hemodialysis (HEMO) study reports on the effect of raising Kt/V_{urea} on a broad range of low molecular weight uremic toxins.1 The HEMO study,2 one of the great pivotal studies in hemodialysis (HD), was itself grounded upon a previous, smaller—but equally important—study in patients with chronic dialysis. The National Collaborative Dialysis Study (NCDS)3 randomized maintenance HD patients to two different (time-averaged) BUN concentrations and two different treatment times. Both the rate of withdrawal from the study for medical reasons and the hospitalization rate were higher in the group of patients with high BUN, whereas no effect of treatment time was seen.

A simple and straightforward conclusion of the NCDS data would have been that BUN concentrations are related to patient outcomes. The authors, however—as stated in the abstract—concluded that occurrence of morbid events is affected by the dialysis prescription.3 A secondary analysis of the same study data, based on kinetic modeling of BUN, popularized the concept of Kt/V_{urea}.4 Eventually, the paradigm of Kt/V_{urea}-driven dialysis prescription prevailed and became the universally used marker of dialysis adequacy. Ever since, Kt/V_{urea} has been subject to criticisms, culminating in a recent debate of its pros and cons.5,6 If a common conclusion would be sought from both texts in spite of the opposite vision they defend, then it could be that Kt/V_{urea} remains a useful baseline metric of certain aspects of dialysis adequacy but that it misses a number of others.

The HEMO study was designed to test the effects of increments in dialysis dose, expressed as Kt/V_{urea} and the level of dialysis membrane flux on patient morbidity and mortality. In the primary analysis of the entire cohort, high-dose hemodialysis providing an average single-pool Kt/V_{urea} of 1.71 provided no benefit over a standard treatment providing a single-pool Kt/V_{urea} of 1.32, although subgroup analysis suggested that survival was increased for women in the high Kt/V_{urea} group. Also, comparison of chronic high-flux dialysis, as defined by higher B-2 microglobulin (B(2)M) clearance, and low-flux dialysis did not significantly alter all-cause mortality. Of note, a secondary analysis showed that mean cumulative predialysis serum B(2)M levels but not dialyzer B(2)M clearance were associated with all-cause mortality.7

The study by Meyer et al. in this issue1 aims to dissect the effects of Kt/V_{urea}-driven dialysis prescription on serum concentrations of a wider panel of small uremic retention solutes. In a cohort of 1281 patients (about two-thirds of the original 1846 study participants), the authors measured predialysis serum levels of various small solutes in the first study year, at least three months after randomization, in an attempt to differentiate the response of high-versus low-dose dialysis expressed as Kt/V_{urea} on individual uremic retention molecule concentrations. Whereas serum concentrations of some solutes were found to be similar between groups, i.e., p-cresyl sulfate and asymmetric dimethyl arginine (ADMA), others were found to be lower in the high Kt/V_{urea} arm. Unsurprisingly, predialysis serum BUN levels were lower, as were levels of trimethylamine oxide (TMAO), indoxyl sulfate, and methylguanidine but, overall, most decreases were not as impressive as would have been expected given the 33% Kt/V_{urea} increment.

Furthermore, along the lines of the original NCDS study, Meyer et al. looked at the association between serum concentrations and outcomes.1 They could not find clear associations between serum levels of uremic retention solutes measured in predialysis samples in the first year of the HEMO study and overall mortality. It should, however, be noted that, for the protein-bound solutes, accurate measurements of free solute concentrations were not available for all patients and that only associations with total solute concentrations were reported. Especially with regards to the cresols, observational studies have shown associations with outcomes especially for the free—i.e., unbound—fraction.8

The assets of this study are that (1) samples were collected prospectively in the context of a randomized controlled trial; (2) although this is a posthoc analysis in a subset of the original study population, the number of samples is large and almost equal per group (643 and 638); and (3) the approach differs from previous analyses by comparing two independent arms rather than performing correlation analyses. All these factors help to minimize sources of external bias.

Although more or less unavoidable with a posthoc analysis, there are, however, also a number of drawbacks: (1) as the...
Hemo study randomized prevalent, and not incident patients, carryover from their treatment before inclusion cannot be excluded; (2) the increment of Kt/Vurea was the result of a mixture of elements, predominantly increases of dialyzer blood flow and dialysis time, but the two factors with more potential to affect protein-bound solutes (dialyzer size and dialysate flow) were much less modulated; (3) dialysis sessions were relatively short, increasing the risk of misinterpreting single-pool Kt/Vurea; and (4) samples were analyzed 10–15 years after collection. Stability of the studied solutes remains uncertain.

How to interpret the main findings of this ancillary study of the Hemo trial? The parent study had already taught us that increasing Kt/Vurea dialysis dose above a threshold of 1.3 did not improve patient outcomes. The current study tells us something about the reasons why. No clear relationship between Kt/Vurea and serum concentrations of the small solutes currently studied, i.e., p-cresyl sulfate, indoxyl sulfate, TMAO, methylguanidine, hippurate, ADMA, SDMA, and methylguanidine, was found, suggesting that achieved Kt/Vurea is not quite informative about the uremic environment of an individual patient. Even more so, relatively large increases in Kt/Vurea failed to greatly reduce the levels of these uremic solutes. For urea, increasing Kt/Vurea by about 30% reduced predialysis serum concentrations by less than 10%. The yield for most other small solutes is much smaller (e.g., TMAO, hippurate, phenylacetylglutamine, SDMA) or even absent (e.g., p-cresyl sulfate, ADMA). Kt/Vurea thus is not a good metric for the effects of changes in dialysis prescriptions on serum concentrations of individual solutes. Nevertheless, Kt/Vurea may remain a useful parameter as it may reflect removal of vital water-soluble compounds like potassium. In addition, recent data suggest toxicity for urea itself, so we cannot completely reject the usefulness of Kt/Vurea.

The authors supported their findings by single-pool kinetic modeling. A discussion of the used kinetic model is warranted. One might assume that a two-pool kinetic model would have been more appropriate, in view of the short dialysis sessions, the complex compartmental pattern of some of the studied molecules, and the major role attributed to intermittency.

The authors validated their model by comparing the results of single- versus double-pool kinetic analysis on methylguanidine, the only compound for which data on compartmental distribution and intercompartmental clearance were available at the moment of submission. The assumption by Meyer et al. that using a two-compartment model probably would not have affected the conclusions dramatically may be correct, but it would be worthwhile to check this thesis, now that detailed data for several protein-bound compounds have become available. Of note, whereas intercompartmental clearances of BUN and methylguanidine are similar, those of protein-bound solutes are often lower by a factor of 4 or more.

Altogether, the data from the study by Meyer et al. strengthen the thesis that the uremic environment is not only determined by dialytic clearance but is equally dependent on the production, adsorption, and/or endogenous metabolism of individual uremic solutes. Moreover, Kt/Vurea does not seem to be the appropriate metric to quantify clearance of “difficult-to-remove” compounds. Once dialytic clearance reaches a certain threshold, Kt/Vurea does not provide useful guidance on how to further optimize treatment for patients with ESRD.

With regards to dialysis, longer and/or more frequent dialysis and/or substantial increments in dialysate flow rates and dialyzer mass transfer-area coefficient, as well as (selective) adsorption, might be appropriate solutions. In addition, however, as dialysis by itself seems to lack a major effect on the concentration of several solutes, focus might shift to other paradigms, such as influencing intestinal generation and absorption or preservation of (residual) renal function.

DISCLOSURES
None.

REFERENCES


