The Patient as a Limit to Dialysis Technology

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Ward *et al.* show in this issue of *CJASN* that Kt/V urea does not improve by increasing the dialysate flow rate in dialyzers in which dialysate flow distribution has been optimized by changes in design (1). Such improved dialyzer designs were developed during the last decade, based on the awareness that poor dialysate flow distribution and the occurrence of preferential dialysate flow paths negatively influenced dialyzer performance (2,3). Improvements mainly consisted in the use of undulated fibers (4), spacer yarns (5,6), and/or increased fiber packing density (7).

To have an idea about dialyzer performance, Michaels defined a patient-independent parameter, *i.e.*, the product of the mass transfer coefficient (K_0) and the membrane surface area (A). This K_0A is a function of dialyzer clearance, K, blood and dialysate flow rate, and is assumed to be constant for a given dialyzer-solute combination (8). However, in clinical practice, the patient-dependent parameter, Kt/V, is most commonly used to indicate dialysis dose in a single treatment. Formulae are available to calculate Kt/V for urea based on the assumption of a single-pool urea model (spKt/V) (9), a double-pool model accounting for a concentration equilibration among the compartments (eKt/V) (10), or by measuring the ionic dialysance (*i.e.*, the purely diffusive clearance) and calculating the distribution volume from anthropometric data (Kt/V_{ID}) (11). To get the target value for Kt/V urea, as recommended by different guidelines (12,13), the focus has been on the maximization of the dialyzer clearance K, since little can be done to change urea distribution volume V, and not much flexibility is available in patients in *in center* facilities to prolong treatment time t. Hence, manufacturers are constantly working on the development of new dialyzer designs that should result in higher clearances, K, and associated higher K_0A values.

Although Michaels (8) initially assumed K_0A being constant, subsequent *in vitro* as well as clinical studies in "nonimproved" dialyzers showed that K_0A increased by 14.7% and 6.7% when dialysate flow was increased from 500 to 800 ml/min, respectively (14,15). This resulted in the use of higher dialysate flow rates to maximize the dialysis dose. Bhimani *et al.* (7) from the same group of the study presented in this issue, previously showed that K_0A no longer increased for higher dialysate flow rates in dialyzers with undulated fibers. Hence, if dialysate flow was increased from 600 up to 800 ml/min with a blood flow rate of 400 ml/min and a hematocrit of 35%, the Michaels equation would predict a clearance increase of only 4%.

In the present paper, Ward *et al.* (1) explored whether the delivered clearance and Kt/V would, as for the predicted ones, not produce a significant increase when enhancing the dialysate flow rate from 600 to 800 ml/min.

To test this hypothesis, in a multicenter randomized clinical trial in 42 patients, the authors compared the delivered single-pool Kt/V as well as the equilibrated and ionic Kt/V at a dialysate flow rate of 600 *versus* 800 ml/min. Each patient underwent either an ABAB or a BABA protocol whereby A and B represented three consecutive dialysis sessions with dialysate flows of 600 or 800 ml/min, respectively. All treatments were performed with Polyflux Revaclear or Revaclear MAX dialyzers (Gambro, Lund, Sweden), which are characterized by both fiber undulations and increased fiber-packing density.

Although the delivered Kt/V urea differed significantly among centers, single-pool, equilibrated, and ionic Kt/V were similar for different dialysate flow rates, regardless of the dialyzes sequence: ABAB or BABA (see Table 1). The measured ionic dialysance, however, which is a pure measure of dialyzer performance, was significantly higher for a dialysate flow rate of 800 ml/min compared with that with 600 ml/min (see Table 1).

As stated by the authors, reducing or at least avoiding an increased dialysate flow has an important economic impact, allowing a reduction in water consumption by 25%. The use of lower dialysate flow rates is of particular interest during nocturnal home hemodialysis, reducing not only the costs for electricity and water consumption, but also avoiding the need to wake up during the night to exchange dialysate concentrate bags. This certainly ameliorates the quality of sleep and thus quality of life. Furthermore, as the need for water will increase in the years to come, also an ecological dimension might be added to the economical considerations.

Besides these positive findings, it should be remarked that Ward *et al.* were only focusing on urea, which is biologically relatively inert (16) and not very representative for other compounds with different kinetic behavior (17,18). Neither the HEMO in hemodialysis (19) nor the ADEMEX study in peritoneal

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Table 1. Different adequacy parameters

Parameter	Dialysate Flow		Remarks[a]
	600 ml/min	800 ml/min	
spKt/V	1.66 ± 0.25	1.63 ± 0.21	Patient dependent (−); single-pool approach (−)
eKt/V	1.37 ± 0.20	1.35 ± 0.18	Patient dependent (−); accounting for multiple compartments (+)
Ionic dialysance (ml/min)	250 ± 17	257 ± 19[b]	Patient independent (+); direct measurement (+)
Kt/V_{ID}	1.46 ± 0.24	1.49 ± 0.35	Partly patient dependent (−); V via anthropometry (−); based on measured dialysance (+)

spKt/V, single-pool Kt/V; eKt/V, equilibrium Kt/V.
[a] −, disadvantage; +, advantage of using this adequacy parameter.
[b] $P < 0.05$ for 800 *versus* 600 ml/min.

dialysis (20), both randomized controlled trials, could demonstrate an improvement in outcome by increasing Kt/V urea above the standards as currently prescribed by guidance bodies (12,13). Because urea moves relatively easily from one compartment to the other and its multicompartmental behavior is relatively limited, it is very unlikely that more significant results would have been obtained with other solutes with more complex kinetic behavior, such as protein-bound compounds or middle molecules. Nevertheless, such an analysis might be worthwhile in the future, especially when other adequacy parameters, such as the postrebound reduction ratio and solute removal in spent dialysate, also could be taken into account.

Nevertheless, based on the available data on urea kinetics, the study by Ward *et al.* shows that continuous technical advances in dialysis devices during the last decades have improved the quality of such devices to such a level that a further increase of the traditional parameters will have no significant impact anymore on dialysis adequacy, at least as calculated as Kt/V urea (16). Likewise, the additional impact of convective ultrafiltration and substitution with the latest version of high-flux membranes becomes less important, as the molecular weight of the larger peptides (so-called middle molecules) became more important (21).

Remarkably enough, although there was in the study by Ward *et al.* (1) no difference in Kt/V_{urea} between dialysate flows of 600 and 800 ml/min, there was a 3% difference in dialysance (Table 1), comparable to the 4% difference in clearance as would be predicted by the Michaels equation (8). Although limited, this variation in dialysance shows that the dialyzer can still be improved, but that "the human body" cannot follow, due to the multicompartmental behavior of most uremic retention solutes. In this context, urea as a marker offers a best-case scenario. Although middle molecules like β2-microglobulin distribute over at least two compartments (22,23) and the shift from the extravascular to the intravascular compartment is hampered, even several guanidino compounds, molecules of a similar metabolic origin as urea and with similar molecular weights and absent protein binding, are distributed over distribution volumes that are up to three times as large as that of urea (17,18).

One might thus conclude that a maximum performance with the traditional dialytic approaches has been reached. If the aim is to further increase toxin removal, probably other options should be considered such as prolonged or more frequent dialysis sessions or a combination of both.

Increasing dialysis time, without changing the total blood or dialysate volume crossing the dialyzer per session, markedly increased removal into the dialysate without changing Kt/V urea (24). This phenomenon is most pronounced for solutes with a larger distribution volume, *e.g.,* methylguanidine and phosphate (24,25), or for solutes with a high resistance against their intercompartmental shifts such as β2-microglobulin (24). This finding was, however, not confirmed for the protein-bound solutes (26). Of note, prolonged dialysis improves left ventricular mass, an important outcome parameter (27). Also Ward *et al.* show that longer dialysis even with subtle differences in dialysis time (210 minutes in center 1 compared with 224 minutes in center 2) resulted in a significantly higher Kt/V, even with a smaller processed blood volume during the longer session (89.6 L *versus* 94.5 L) (1).

Increasing dialysis frequency, while keeping total treatment time constant, has only some impact on dialysis adequacy for solutes distributed in a small volume (25). Remarkably, daily dialysis decreased the concentration of protein bound solutes (28), and outcome improved with more frequent dialysis (29).

A restriction to a more widespread use of those frequent and prolonged regimens is the relatively tight restraint upon dialysis times in *in center* hemodialysis. In this way, home hemodialysis or night self-dialysis can offer more flexibility and better-tailored schemes in function of the needs of the patient, while at the same time offering more dialysis adequacy.

In conclusion, the study of Ward *et al.* (1) clearly demonstrates no impact on dialysis adequacy of increasing the dialysate flow rate in dialyzers even with an improved design. Although the findings were purely based on urea removal and should be confirmed by studying the removal of other solutes with a more complex compartmental behavior, improved dialyzer designs may be associated with a significant economical and ecological beneficial impact and higher quality of life for the patient dialyzing at home.

Disclosures

None.

References

1. Ward RA, Idoux JW, Hamdan H, Ouseph R, Depner TA, Golper TA: Dialysate flow rate and delivered Kt/V_{urea} for dialyzers with enhanced dialysate flow distribution. *Clin J Am Soc Nephrol* 6: 2235–2239, 2011
2. Eloot S, D'Asseler Y, De Bondt P, Verdonck R: Combining SPECT medical imaging and computational fluid dynamics for analyzing blood and dialysate flow in hemodialyzers. *Int J Artif Organs* 28: 739–749, 2005
3. Ronco C, Brendolan A, Crepaldi C, Rodighiero M, Scabardi M: Blood and dialysate flow distributions in hollow-fiber hemodialyzers analyzed by computerized helical scanning technique. *J Am Soc Nephrol* 13[Suppl 1]: S53–S61, 2002
4. Ronco C, Bowry SK, Brendolan A, Crepaldi C, Soffiati G, Fortunato A, Bordoni V, Granziero A, Torsello G, La Greca G: Hemodialyzer: From macro-design to membrane nanostructure; the case of the FX-class of hemodialyzers. *Kidney Int Suppl* 126–142, 2002
5. Poh CK, Hardy PA, Liao Z, Huang Z, Clark WR, Gao D: Effect of spacer yarns on the dialysate flow distribution of hemodialyzers: A magnetic resonance imaging study. *ASAIO J* 49: 440–448, 2003
6. Ronco C, Scabardi M, Goldoni M, Brendolan A, Crepaldi C, La Greca G: Impact of spacing filaments external to hollow fibers on dialysate flow distribution and dialyzer performance. *Int J Artif Organs* 20: 261–266, 1997
7. Bhimani JP, Ouseph R, Ward RA: Effect of increasing dialysate flow rate on diffusive mass transfer of urea, phosphate and beta2-microglobulin during clinical haemodialysis. *Nephrol Dial Transplant* 25: 3990–3995, 2010
8. Michaels AS: Operating parameters and performance criteria for hemodialyzers and other membrane-separation devices. *Trans Am Soc Artif Intern Organs* 12: 387–392, 1966
9. Daugirdas JT: Second generation logarithmic estimates of single-pool variable volume Kt/V: An analysis of error. *J Am Soc Nephrol* 4: 1205–1213, 1993
10. Daugirdas JT, Schneditz D: Overestimation of hemodialysis dose depends on dialysis efficiency by regional blood flow but not by conventional two pool urea kinetic analysis. *ASAIO J* 41: M719–M724, 1995
11. Watson PE, Watson ID, Batt RD: Total body water volumes for adult males and females estimated from simple anthropometric measurements. *Am J Clin Nutr* 33: 27–39, 1980
12. National Kidney Foundation: Clinical Practice Guidelines for Hemodialysis Adequacy, update 2006. *Am J Kidney Dis* 48: S2–S90, 2006
13. Tattersall J, Martin-Malo A, Pedrini L, Basci A, Canaud B, Fouque D, Haage P, Konner K, Kooman J, Pizzarelli F, Tordoir J, Vennegoor M, Wanner C, ter Wee P, Vanholder R: EBPG guideline on dialysis strategies. *Nephrol Dial Transplant* 22[Suppl 2]: ii5–21, 2007
14. Leypoldt JK, Cheung AK, Agodoa LY, Daugirdas JT, Greene T, Keshaviah PR: Hemodialyzer mass transfer-area coefficients for urea increase at high dialysate flow rates. The Hemodialysis (HEMO) Study. *Kidney Int* 51: 2013–2017, 1997
15. Ouseph R, Ward RA: Increasing dialysate flow rate increases dialyzer urea mass transfer-area coefficients during clinical use. *Am J Kidney Dis* 37: 316–320, 2001
16. Johnson WJ, Hagge WW, Wagoner RD, Dinapoli RP, Rosevear JW: Effects of urea loading in patients with far-advanced renal failure. *Mayo Clin Proc* 47: 21–29, 1972
17. Eloot S, Torremans A, de Smet R, Marescau B, De Wachter D, De Deyn PP, Lameire N, Verdonck P, Vanholder R: Kinetic behavior of urea is different from that of other water-soluble compounds: The case of the guanidino compounds. *Kidney Int* 67: 1566–1575, 2005
18. Eloot S, Torremans A, de Smet R, Marescau B, De Deyn PP, Verdonck P, Vanholder R: Complex compartmental behavior of small water-soluble uremic retention solutes: Evaluation by direct measurements in plasma and erythrocytes. *Am J Kidney Dis* 50: 279–288, 2007
19. Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, Allon M, Bailey J, Delmez JA, Depner TA, Dwyer JT, Levey AS, Levin NW, Milford E, Ornt DB, Rocco MV, Schulman G, Schwab SJ, Teehan BP, Toto R: Hemodialysis (HEMO) Study Group: Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 347: 2010–2019, 2002
20. Paniagua R, Amato D, Vonesh E, Correa-Rotter R, Ramos A, Moran J, Mujais S: Mexican Nephrology Collaborative Study Group: Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. *J Am Soc Nephrol* 13: 1307–1320, 2002
21. Meert N, Eloot S, Waterloos MA, Van Landschoot M, Dhondt A, Glorieux G, Ledebo I, Vanholder R: Effective removal of protein-bound uraemic solutes by different convective strategies: A prospective trial. *Nephrol Dial Transplant* 24: 562–570, 2009
22. Leypoldt JK, Cheung AK, Deeter RB: Rebound kinetics of beta2-microglobulin after hemodialysis. *Kidney Int* 56: 1571–1577, 1999
23. Stiller S, Xu XQ, Gruner N, Vienken J, Mann H: Validation of a two-pool model for the kinetics of beta2-microglobulin. *Int J Artif Organs* 25: 411–420, 2002
24. Eloot S, van Biesen W, Dhondt A, Van de Wynkele H, Glorieux G, Verdonck P, Vanholder R: Impact of hemodialysis duration on the removal of uremic retention solutes. *Kidney Int* 73: 765–770, 2008
25. Eloot S, van Biesen W, Dhondt A, de Smet R, Morescau B, De Deyn PP, Verdonck P, Vanholder R: Impact of increasing haemodialysis frequency versus haemodialysis duration on removal of urea and guanidino compounds: A kinetic analysis. *Nephrol Dial Transplant* 24: 2225–2232, 2009
26. Basile C, Libutti P, Di Turo AL, Casino FG, Vernaglione L, Tundo S, Maselli P, De Nicolò EV, Ceci E, Teutonico A, Lomonte C: Removal of uraemic retention solutes in standard bicarbonate haemodialysis and long-hour slow-flow bicarbonate haemodialysis. *Nephrol Dial Transplant* 26: 1296–1303, 2011
27. Culleton BF, Walsh M, Klarenbach SW, Mortis G, Scott-Douglas N, Quinn RR, Tonelli M, Donnelly S, Friedrich MG, Kumar A, Mahallati H, Hemmelgarn BR, Manns BJ: Effect of frequent nocturnal hemodialysis vs conventional hemodialysis on left ventricular mass and quality of life: A randomized controlled trial. *JAMA* 298: 1291, 2007
28. Fagugli RM, de Smet R, Buoncristiani U, Lameire N, Vanholder R: Behavior of non-protein-bound and protein-bound uremic solutes during daily hemodialysis. *Am J Kidney Dis* 40: 339–347, 2002
29. Chertow GM, Levin NW, Beck GJ, Depner TA, Eggers PW, Gassman JJ, Gorodetskaya I, Greene T, James S, Larive B, Lindsay RM, Mehta RL, Miller B, Ornt DB, Rajagopalan S, Rastogi A, Rocco MV, Schiller B, Sergeyeva O, Schulman G, Ting GO, Unruh ML, Star RA, Kliger AS: In-center hemodialysis six times per week versus three times per week. *N Engl J Med* 363: 2287–2300, 2010

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