"Artificial" Hemodialysis Versus "Natural" Hemofiltration

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Because the native kidney is a filter and does not engage in the process of dialysis, long-held beliefs in the superiority of blood filtration for eliminating uremic toxins have rarely been challenged. What could be better than the divine prototype?

In the early 1960s, shortly after hemodialysis (HD) was first applied as a life-sustaining therapy for patients with chronic irreversible kidney failure, it became clear that the astonishing life-saving effects of HD could not be extended to restore a normal quality of life. Patients continued to suffer from lethargy, poor appetite, occasional nausea and vomiting, and inability to concentrate and function on a par with coworkers. Mortality rates were, and continue to be, much higher than in the general population. The logical answer to the "why" question was that the therapy was incomplete. However, attempts during the late 1960s and early 1970s to increase the intensity or "dose" of dialysis with higher blood and dialysate flow rates, larger membranes, and longer treatment times failed to bring about the desired improvement in outcome. Although early work with dialysis was hampered by adverse effects of the dialysis itself, the original pioneers (as well as some present-day dialysis clinicians) concluded that inadequate removal of toxic large molecules was responsible at least in part for these disappointing results.[1] Early reports of new highly permeable membranes made from synthetic polyacrylonitrile that could cure uremic neuropathy, a uremic complication previously thought to be reversed only by renal transplantation, spurred efforts to develop membranes and delivery systems aimed at removing larger molecules.[2]

Hollow fiber membranes are now available across a spectrum of porosities that range from a tight low-flux configuration that excludes filtration of β_2-microglobulin (molecular weight, 11,800 Da) and all solutes heavier than 10,000 Da, to membranes used for plasmapheresis that offer little or no resistance to filtration of albumin (molecular weight, 66,000 Da). Typical high-flux membranes that are increasingly used for HD in developed countries have hydraulic permeabilities 20 to 40 times that of previously used low-flux membranes and consequently require ultrafiltration control devices to protect the patient from sudden gains and losses of fluid during treatments. The permeability of high-flux membranes to larger molecules is also markedly enhanced, allowing finite clearances of β_2-microglobulin in the 30- to 40-mL/min range compared to near 0 for conventional low-flux membranes. Despite this advance in membrane construction, a randomized controlled trial (RCT) published in 2002 from the Hemodialysis (HEMO) Study group failed to detect a significant clinical advantage of high-flux membranes.[3] The HEMO Study, which was designed to detect improvements in several outcome measures, including survival, remains the most definitive RCT conducted to date. It showed that HD with high-flux membranes conferred only a small and insignificant survival advantage over standard-flux membranes in a large cohort of patients followed for an average of 2.8 years in 72 dialysis clinics scattered across the United States. A more recent smaller RCT of high-flux HD in Europe also failed to show a significant benefit after a minimum of 3 years of follow-up.[4] However all of the above were studies of dialysis, not filtration.

Filtration has an intrinsic capacity to remove larger molecular species even when the membrane is identical to that used for HD.[5] Hydraulic pressure applied across the membrane forces larger molecules to traverse membrane pores at a more rapid rate than is possible by simple diffusion. This understanding and the above-described yearning to mimic the "natural" glomerular filter encouraged the dialysis industry to develop and manufacture hemofiltration (HF) equipment with more porous membranes that could replace the dialysis machines and membranes that currently dominate the market. However, the thought of

Address correspondence to Thomas A. Depner, MD, University of California Davis Medical Center, Division of Nephrology, 4150 V St, Ste 3500, Patient Support Services Bldg, Sacramento, CA 95817. E-mail: tadepner@ucdavis.edu

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infusing many gallons of sterile fluid directly into the bloodstream during each treatment and, conversely, directly removing by filtration an equal amount of fluid from the body and sending it down the drain, might have caused early investigators to pause, even if they had in hand the highly permeable membranes and control devices necessary to make therapeutic HF work.

Early attempts to show a clinical advantage of HF were hampered by an excessive focus on large-molecule clearance; inadequate small-molecule clearance probably accounted for worse HF outcomes in some of the studies.[6] Clearly, one must first assure small-molecule clearance before attempting to improve outcomes by removing larger solutes.[7] Later observational studies of HF that provided adequate small-molecule clearance, measured as Kt/V_{urea}, suggested a benefit of HF when compared to HD.[8] However, a recent review published in the *American Journal of Kidney Diseases* of 18 RCTs comparing filtration with dialysis concluded that the trials were not adequately powered to recommend one modality over the other.[9] Hemodiafiltration (HDF), a modality that combines diffusion and filtration within the same hollow fiber device, was associated with a significantly higher mortality among 4 clinical trials totaling 336 patients. The authors stated that for HF, HDF, and HD, "significant differences in the clinically important outcomes have not been shown. . . . "[9] In a related area, a large US study published this year failed to show a survival advantage of continuous HDF compared to intermittent HD for critically ill patients with acute kidney injury.[10] The collective effect of these reports showing no benefit of HF or HDF have dampened enthusiasm and caused providers in the United States to all but abandon HF as a substitute for long-term HD, despite availability of Medicare funding. Providers were probably relieved by these negative findings because, if mandated by clinical evidence, over 15,000 existing dialysis clinics throughout the world would require retooling to replace HD with HF, a method that has not advanced as far as dialysis in terms of ease of use, cost efficiency, and patient safety.

Most recently, in the current issue of *AJKD*, Santoro et al report improved survival and other outcome measures in a small RCT in Italy of thrice-weekly HF versus HD.[11] In the HF arm, this study used on-line generation of predilution replacement fluid, which for an average-sized adult patient would amount to approximately 80 L infused intravenously per treatment, three times weekly. Both dialysate and replacement fluids met ultrapure standards and were warmed to 37°C, mitigating a source of previous controversy about low temperatures stabilizing blood pressure during HF.[12] Membranes for dialysis and filtration were identical in their chemical composition (polyamide), but the HD membranes were small-pore "low-flux" membranes that were essentially impermeable to, and therefore incapable of removing, β_2-microglobulin and similar large molecules. Selection of tight membranes in the HD group allowed a maximum separation of large-molecule clearance, which is the most significant and perhaps only difference between the 2 modalities, but it did not allow a comparison of HF to high-flux HD. The patient numbers were small, starting with 32 and ending with 11 patients after 3 years in each arm of the study, so the seemingly significant improvement in survival with HF is hazardous to interpret and runs the risk of misleading the clinician.[13]

Although the natural kidney is a filter, it wasn't always that way. On the evolutionary scale, primitive organisms relied on the infinite dialysate of the primordial sea to dispose of their wastes or end products of metabolism. They also developed highly specialized membrane transporters to gather and keep substances vital to their existence. For example, existing bacteria and fungi have specialized transporters with high affinity for environmental iron, which is vital to energy transfer within the organism.[14] As animals left the expanse of the sea, they were challenged to develop a substitute system to allow immediate disposal of metabolites and to quickly remove unwanted xenobiotics that might be ingested with their food and drink. Some students of evolution believe that glomerular filtration was developed to satisfy that need.[15]

Analogous to the function of cell membranes, the purpose of the glomerular filter is to separate large from small particles, including soluble molecules. The tremendous filtration rate of metanephric kidneys allowed immediate disposal of unknown and unwanted solutes while specialized transporters, previously developed for vital solute recovery and retention, were utilized by the tubular cell membranes.[16,17] From this point of view, diffu-