Technological Advances in Renal Replacement Therapy: Five Years and Beyond

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The worldwide epidemic of chronic kidney disease shows no signs of abating in the near future. Current dialysis forms of renal replacement therapy (RRT), even though successful in sustaining life and improving quality of life somewhat for patients with ESRD, have many limitations that result in still unacceptably high morbidity and mortality. Transplantation is an excellent option but is limited by the scarcity of organs. An ideal form of RRT would mimic the functions of natural kidneys and be transparent to the patient, as well as affordable to society. Recent advances in technology, although generally in early stages of development, might achieve these goals. The application of nanotechnology, microfluidics, bioreactors with kidney cells, and miniaturized sorbent systems to regenerate dialysate makes clinical reality seem closer than ever before. Finally, stem cells hold much promise, both for kidney disease and as a source of tissues and organs. In summary, nephrology is at an exciting crossroad with the application of innovative and novel technologies to RRT that hold considerable promise for the near future.


The ongoing worldwide epidemic of chronic kidney disease (CKD) includes ESRD. According to recent US Renal Data System estimates, more than 900,000 patients worldwide have ESRD and are on renal replacement therapy (RRT) (1). The majority of these patients are on intermittent, diffusion-based hemodialysis (HD), with only a relatively small fraction able to receive kidney transplants because of the scarcity of available donor organs.

Even though dialysis is touted as the only currently available successful therapy that replaces the functions of an organ ex vivo, it has several limitations. The advent of clinical dialysis in the 1950s has had a huge impact on the way in which ESRD and acute kidney failure are managed, but several decades later, the morbidity and mortality in patients with ESRD remain unacceptably high (1). One possible reason is that the equivalent clearance provided by three-times-a-week conventional HD or typical continuous ambulatory peritoneal dialysis (PD) is barely 15 to 20 ml/min, and the treatment by any criterion is unphysiologic (2). At the same time, the quality of life of patients who are on dialysis has remained suboptimal, and the cost of these procedures has remained high.

Several attempts have been made to prove intramuscularly the efficiency of dialysis and outcomes in patients. In HD, these attempts include more biocompatible membranes, high-flux and high-efficiency membranes, more frequent and longer duration of dialysis, use of convective forms of therapy, and use of more user-friendly delivery systems. In PD, introduction of automated cyclers has improved convenience of the technique for some patients, increased the practical volume of dialysate, and, therefore, increased solute clearance and ultrafiltration capacity; however, none of these advances has had a substantial impact on patient outcomes.

An ideal form of RRT would mimic the kidneys completely. It would be continuously operating; would remove solutes with a molecular weight spectrum similar to that of the kidneys; would remove water and solutes on the basis of individual patient needs; and would be biocompatible, wearable, and ideally implantable. It would also be low cost, reliable, and safe. A few years ago, these goals would have seemed impossible to achieve, but with advances in the sciences of nanotechnology and microfluidics, renal replacement of the future may come closer to this ideal (3–5).

Nanotechnology Applications

Nanotechnology, as defined by Drexler (6), refers to atomically precise functional machine systems developed on the scale of the nanometer (i.e., one-billionth of a meter). This technology is an area of intense research, with a national commitment by the US government to promote research in this field. The precision provided by nanotechnology will make possible the design of tools that will operate at the molecular level. Nanomedicine is the application of nanotechnology for the advancements of biomedical research and is defined as the monitoring, repair, construction, and control of human biologic systems at the molecular level by use of engineered nanodevices and nanostructures. The number of potential applications to RRT is many, and a few major ones are discussed next.
**Human Nephron Filter**

Nissenson and colleagues (7,8) have proposed the human nephron filter (HNF) as a novel mode of RRT for patients with ESRD. The HNF consists of two membranes that operate in series within one cartridge. The first membrane is called the G membrane and is analogous to the glomerular membrane in the nephron. It mimics the functions of the glomerulus by using convective transport to generate plasma ultrafiltrate that contains solutes that approach the molecular weight of albumin. The second membrane is called the T membrane and mimics the functions of the tubule. It is molecularly engineered and selectively reclaims convectively the designated solutes to maintain homeostasis. No dialysate is used in the system.

The blood is pumped at approximately 100 ml/min across the G membrane after access is obtained. The entire thickness of the membrane is approximately 1 mm, with the total surface area needed just over one tenth of a square meter. Operating 12 h/d, 7 d/wk, it can provide the equivalent of 30 ml/min GFR.

The T membrane is supported on a substrate and contains molecularly engineered pores that make it unique. Total surface area needed is just over one-hundredth of a square meter. The membrane contains approximately $1.6 \times 10^{16}$ pores, 1 to 5 nm apart. The pores will come in different sizes and shapes, and eventually a pore library will be available to permit custom membranes to be produced to meet individual needs. There are key differences between molecularly engineered membranes and conventional polymer membranes: Molecularly engineered membranes contain a predetermined number and size of pores that are atomically engineered and have specific interactions with solutes that provide selective transport characteristics to the membrane. The active filtration layer is ultrathin—approximately 2.5 nm—approaching the size of a single molecule. In contrast to these molecularly engineered membranes, the conventional polymer membranes are thick, have unselective transport of solutes, and have a wide distribution of pore sizes and numbers that are difficult to control.

The G membrane discriminates between solutes on the basis of molecular size. The ultrafiltrate formed after blood passes through the G membrane contains both desirable and undesirable solutes. The ultrafiltrate passes over the T membrane, which reclaims most of the desirable solutes and rejects the undesirable ones. The T membrane is able to differentiate because each of its pores is a designed discriminator and is made up of multiple unique pores. The pores were designed to reabsorb all of the desirable solutes and reject the undesirable ones. Pores with similar radii can be designed to have very different and selective transport properties.

Modeling studies of the performance of the HNF for urea, β2-microglobulin, and a variety of other solutes have been performed. The amount of water passed to waste could be varied, depending on the volume status of the patient, and a very high efficiency of water recovery (more than 99%, as with the native kidney) is assumed to be achieved. The efficiency of urea removal is assumed to be 100% in this model, with complete rejection of urea reabsorption by the T membrane. With an assumed blood flow of 100 ml/min, urea clearance is calculated to be 62.8 ml/min.

To compare conventional HD with RRT that uses the HNF, we modeled dialysis with a 4-h treatment three times a week (Monday, Wednesday, and Friday), no residual kidney function, and a dialyzer with a urea clearance of 277 ml/min at a Qb of 300 ml/min and a Qd of 500 ml/min. For the HNF model, the assumption was no residual kidney function, a 12-h treatment 7 d/wk, a blood flow of 100 ml/min, and a 100% rejection of urea by the T membrane as noted previously. Simulating 30 ml/min GFR would result in a time-averaged urea concentration (TAC) in the HNF-modeled patient of approximately 27 mg/dl, with minimal fluctuations of blood urea nitrogen throughout a weekly cycle. By contrast, the thrice-weekly dialysis simulation yields a TAC of 67.3 mg/ml, with wide excursions of blood urea nitrogen reflecting the intermittent nature of the treatment. If the HNF were to run continuously, then the TAC would fall to normal levels.

Similar simulations were performed for β2-microglobulin, assuming free passage of β2-microglobulin through the G membrane and 100% rejection by the T membrane. For the β2-microglobulin studies, the rate of β2-microglobulin production was assumed to be 0.17 mg/min, and the rate of clearance for the Fresenius dialyzer was assumed to be 78 ml/min. The HNF system can reduce and sustain low levels of β2-microglobulin compared with other dialytic approaches. With 12-h, 7-d/wk treatment, levels of β2-microglobulin are predicted to approach normal.

Modeling was also done to assess the removal of some of the other key substances, including sodium, potassium, calcium, magnesium, phosphorus, and bicarbonate, under a variety of clinical conditions. In a 70-kg patient on a normal diet, the initial HNF system is capable of maintaining balance for all of these substances, except bicarbonate, which may need additional supplementation. Other solutes of various molecular size will also be removed, many of which are not commonly measured; thus, patients will need close monitoring. The experience to date with daily, overnight diffusion dialysis would suggest that this monitoring is unlikely, but careful consideration of this possibility will be necessary when clinical trials with the HNF are conducted. The combined use of sensors in the device (e.g., pH, ion-selective electrodes), preclinical evaluation, and empirical observation is expected to allow us to formulate appropriate usage variables.

An additional challenge with the proposed system will be the approach to anticoagulation when the device is in use, because continuous contact with the circulation will be obtained. Initial low-level systemic anticoagulation will be achieved with warfarin or heparin. The surfaces of the pores in the T membrane, however, were designed to have the ability to bond covalently to anticoagulant substances, such as heparin and thrombomodulin. This approach may minimize or eliminate the need for administration of anticoagulants.

**Silicone Nanopore Membranes**

The conventional membranes currently in use are characterized by variation in both pore size and distribution and are relatively thick. In addition, the pores at the end of the cylindrical fibers tend to be round. The pores in these membranes have atomically engineered and have specific interactions with solutes that provide selective transport characteristics to the membrane. The active filtration layer is ultrathin—approximately 2.5 nm—approaching the size of a single molecule. In contrast, these molecularly engineered membranes, the conventional polymer membranes are thick, have unselective transport of solutes, and have a wide distribution of pore sizes and numbers that are difficult to control.

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are formed by extrusion and solvent-casting techniques, and their geometry and surface chemistry are determined by the chemistry of the polymers used in the synthesis and the fluid dynamics of the casting process; however, this geometry and surface chemistry do not provide the optimal filtration function for several reasons. Large molecular weight molecules are retained because of the dispersion of pore size. Such dispersion can be corrected for but at the cost of hydraulic permeability. The hydraulic permeability of a round pore will depend on the 4th power of the radius of that pore; however, if a pore is slit shaped rather than round, then the hydraulic permeability will depend on the long dimension of the pore. At the same time, the steric hindrance will still be determined by the smallest dimension of the pore. The glomerular membrane provides electrostatic hindrance in addition to the steric hindrance. Many substrates have an anionic surface charge at physiologic pH. This net charge density on a microfluidic substrate in contact with an aqueous solution gives rise to an electric double layer called the Debye layer (9), which has thickness that can be on the same scale as the nanopore size and can contribute to the selective property of these membranes by rejecting charged solutes. Recently, Fissell et al. (10) described in vitro results with such a membrane.

Leonard and colleagues (11-13) proposed membraneless dialysis by application of the principles of microfluidics. This approach is based on the principle that at low Reynolds number, two miscible liquids can flow in parallel in direct contact with each other without significant mixing. This property permits diffusive transport to take place as in conventional dialysis but without the presence of a dialysis membrane. Elimination of the dialysis membrane and its limiting features offers many potential advantages to solute removal. This theoretical construct holds promise for future dialysis devices. An initial application focused on ultrafiltration, packaged in a wearable device, has been proposed by these investigators as a starting point (14).

Living Membranes and Bioartificial Kidney

A major limitation of current membranes is the tendency to occlude over time because of protein deposition and thrombus formation. This tendency limits the life of the cartridge and the efficiency of the process. A technique that uses endothelial cell–lined conduits with microelectromechanical systems (MEMS) has made advances in this field. Another limitation of current technology is the lack of the biologic functions of the tubule, including metabolic, reclamation, and endocrine functions. Humes and colleagues (15–17) proposed living membranes that incorporate renal tubule cells to overcome this problem. This technique depends on the ability to isolate and grow adult tubular cells in culture. These cells are subsequently grown along the inner surface of the fibers of the standard hemofiltration cartridge. This tubule cell cartridge is then placed in series with a conventional hemofilter, constituting a bioartificial kidney called a renal assist device. In vitro and ex vivo tests of renal assist devices have been conducted of animals and critically ill patients, with promising results that include better cardiovascular and hemodynamic parameters and improved survival (18–20). Of particular interest is the potential differential beneficial effect in patients with acute kidney injury associated with sepsis (21–25).

Nanoelectronics

For creation of a fully automated, implantable dialysis system, accurate real-time assessment of fluid/electrolyte/acid-base status is needed. In addition, this detection system must be miniature in size. MEMS technology is a miniature component system that integrates sensors, actuators, and electronics and is proposed as a more accurate, reliable, and yet miniature method of assessing fluid status and other critical variables. Applying MEMS to dialysis systems might provide the analytical platform needed (26,27).

Wearable Artificial Kidney

Gura and colleagues (28,29) have been developing a wearable artificial kidney (WAK) that uses existing technology coupled with miniaturization. This HD system uses a sorbent system that regenerates dialysate, reminiscent of the peritoneal-based wearable system developed by Lee and Roberts (30). The WAK is the first of the wearable HD concepts that has undergone clinical trials. Preliminary results suggest that adequate small solute and water removal can be accomplished with this device. Most recently, Gura et al. (30) reported on removal of phosphate and β2-microglobulin using the WAK in eight long-term HD patients. Patients were fitted with a wearable HD device for 4 to 8 h with excellent tolerance to the treatment. On average, 99.8 ± 63.1 mg of β2-microglobulin was removed, with a mean clearance of 11.3 ± 2.3 ml/min, and an average of 445.2 ± 326 mg of phosphate was removed, with mean plasma phosphate clearance of 21.7 ± 4.5 ml/min. These clearances compared favorably with mean urea and creatinine plasma clearances (21.8 ± 1.6 and 20.0 ± 0.8 ml/min, respectively). These results confirm that such a device not only is well tolerated by patients but also can achieve adequate removal of larger as well as smaller solutes.

Ronco et al. (31) described a new wearable system for continuous PD called Vicenza WAK (ViWAK). The system uses a cartridge that contains polystyrenic resin that completely removes β2-microglobulin and ion exchange resin that removes urea and creatinine. Circulating 12 L of exhausted PD solution through the experimental adsorption unit at the rate of 20 ml/min provided 11.2 L of net solute clearance. ViWAK is designed to be used 10 h during the day, can potentially reduce the number of exchanges compared with continuous ambulatory PD, and uses less fluid than ambulatory PD. REDY sorbent cartridge has been used by other investigators to regenerate dialysate similar to the composition of commercially available peritoneal dialysate using spent dialysate (32). Although WAK has the potential to become the preferred from of treatment for ESRD, many improvements are still required.

Stem Cells

Stem cells are characterized by their ability to self-replicate and undergo multilineage differentiation to produce functional tissue. The stems cells are broadly divided into embryonic and...
adult categories, depending on their source, with subtle differences in the two categories. Stem cells hold promise in multiple gels, including acute and chronic renal disease, and as a potential source of tissues and organs (33); however, ethical concerns surrounding their use may require much to be done before stem cells can live up to their full potential.

Conclusions
For patients with ESRD, the past four decades have provided many miracles. Countless millions throughout the world would have died if not for the availability of RRT. Unfortunately, however, mortality, morbidity, and quality of life remain unacceptable, and new treatment technologies and paradigms are sorely needed. The past 5 yr has seen a resurgence of interest in truly transforming the technological approach to ESRD, and, in the years to come, we should see many of the advances described coming into clinical reality.

Disclosures
None.

References
