An Integrated Membrane/Sorbent PD Approach to a Wearable Artificial Kidney

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Abstract— **A wearable artificial kidney has been the dream of patients, physicians, and scientists for many years. Most systems developed to date incorporate some combination of membranes, sorbents, enzymes, and/or cells, which are used to mimic the filtration and metabolic aspects of the kidney. These systems aim to provide equivalent or better treatment than traditional dialysis while allowing more freedom and better quality of life to patients. Nevertheless, many challenges have yet to be solved in creating a dialysis device that is small, lightweight, ergonomic, effective, and safe.**

Wearable systems based on peritoneal dialysis avoid the risk of sepsis inherent in repeatedly accessing the bloodstream and use the peritoneal cavity as a built-in dialysate reservoir. Continuous-flow PD systems offer the advantage of improved peritoneal transport due to better mixing and reduced boundary layer thickness. The use of sorbents to regenerate PD fluid may enable dialysate solution to be used for an extended period of time, but currently available sorbent dialysis systems are too large and heavy for use in a wearable system.

A new approach to a PD-based wearable artificial kidney entails the use of specialized membranes in combination with sorbents. Placement of sorbents in the shell side of hollow fiber device has a number of advantages. This configuration reduces the power requirement by reducing the effective "column height" of the sorbent particles. Membranes protect the peritoneal cavity from particulates and eliminate the need for alumina to retain urease. Ion-rejecting membranes prevent excessive adsorption of Ca and Mg by the ammonia sorbent, and improve the sorbent capacity for ammonia by retaining ions that would otherwise compete for binding sites. When combined with improvements in sorbent capacity, miniaturized pumps, and batteries, the membrane/sorbent system offers the potential for a truly wearable system.

Keywords— **Wearable artificial kidney, dialysis, extracorporeal treatment, membrane, sorbent.**

I. INTRODUCTION

Kidney failure, particularly chronic kidney disease stage 5 (CKD-5), results in an inability to remove water and by-products of metabolism, maintain acid-base balance, and control electrolyte levels. Currently patients with CKD-5 who do not receive transplants are treated to remove water and toxins that build up once the kidneys can no longer properly filter the blood. Most CKD-5 patients are treated by hemodialysis (HD), in which blood is circulated from the body to an external membrane filter where toxins diffuse into the dialysis fluid which flows to the drain. Other patients use peritoneal dialysis (PD), in which sterile fluid is infused into the abdominal cavity, and toxins diffuse into this fluid across the peritoneal membrane, which acts as a natural dialyzer. After a prescribed dwell time, the PD fluid is then drained and discarded.

While both modes of dialysis can be effective, both are labor intensive and time-consuming. HD requires patients to visit clinics 3 times per week and remain tethered to large dialysis machines for 3.5-4.5 hours per treatment. While PD provides the patient more autonomy; the repeated filling and draining of fluid can be cumbersome and inconvenient. Additionally, both of these treatments are periodic in nature unlike the kidney, which filters blood continuously. For these reasons, researchers have sought to develop a safe and continuous wearable system for treating kidney failure.

II. HISTORY

In order to give ESRD patients a better quality of life and possibly a better treatment, physicians and scientists have been developing the idea of a "wearable artificial kidney" for more than 30 years. One of the first reports of a wearable artificial kidney came in 1976 [1], where a 20 L case contained blood and dialysate pumps, rechargeable batteries, tubing, a dialyzer, and a charcoal regeneration module. The weight of this initial system was 17 kg. This system was used to treat 5 patients and resulted in the daily removal of 14-20 g urea, 1.5-2.0 g creatinine, and 30-55 meq of potassium. Since this initial study, many strides have been made towards making a miniaturized dialysis device. Researchers have taken different approaches by using membranes, sorbents, enzymes, and even kidney cells.

III. RECENT ADVANCES AND CURRENT OPTIONS

Kidney failure results in the retention of various metabolite compounds that can exert some toxicity. These compounds in the blood can be freely water soluble or protein bound. Almost 100 compounds have been identified as uremic toxins that are found at high concentrations in patients with kidney failure compared to healthy controls [2]. Regular dialysis treatment removes these toxins.

O. Dössel and W.C. Schlegel (Eds.): WC 2009, IFMBE Proceedings 25/VII, pp. 729–732, 2009.
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While some investigators have attempted to mimic the filtration and reabsorption performed by the human kidney using membranes in series [3], or to more closely duplicate the kidney by incorporating renal cells in a bioartificial kidney [4], the most widely studied approach to a wearable artificial kidney has been to use sorbents to continually regenerate a small volume of dialysate. Sorbents have been used in other medical devices to remove toxic compounds. For example, sorbent columns, containing activated carbon, ion exchangers, or other sorbents, have been developed to treat chronic and acute liver failure [5, 6]. Alternatively, sorbents could be ingested by the patient as is the case for a commercially available ion exchange resin taken orally to treat hyperkalemia (Sanofi-Aventis, Bridgewater, NJ). Additionally, enzymes could be encapsulated with sorbents, such that toxins could react with the enzyme to generate a compound which is removed by the sorbent [7].

Sorbent cartridges for dialysate regeneration (Redy system) were developed by SORB Technologies (Oklahoma City, OK) in the 1970's. These cartridges contain a supported enzyme (urease) from jack beans for degrading urea into ammonium carbonate, zirconium based ion exchangers which remove ionic compounds, such as phosphate, calcium, magnesium, and ammonium, and an activated carbon to remove creatinine and other organics. The Redy system was developed to be a dialysis treatment that could be performed using only 6 L of tap water, instead of a constant supply of highly purified water. These sorbent cartridges are too large as-is for a wearable device, but the sorbents contained within the cartridges have been used in studies aimed at creating a miniaturized dialysate regenerating system.

In 2007 a pilot study investigated the use of sorbent columns to regenerate a small volume of dialysate for eight patients undergoing hemodialysis treatment [8]. For this study, a belt system was developed to carry sorbents as well as a dialyzer, pumps and battery. The pumps recirculated blood and dialysate in a low-flow HD treatment and the patients were free to move around. During this pilot study, no adverse events were reported. The device weighed approximately 5 kg, but the reported amount of urea and creatinine removal was much less than a typical HD session.

Because continuous blood access is difficult and hazardous, the sorbents could be also applied to a peritoneal dialysis system. In this case, peritoneal dialysis fluid would circulate through a series of sorbent columns for regeneration and back to patient's abdominal cavity. This kind of system would be safe enough to wear continuously and without medical supervision. It would also allow patients to perform normal daily activities without out the burden of multiple fill and drain cycles.

IV. A PERITONEAL DIALYSIS BASED WEARABLE DEVICE

Creating a device that will regenerate peritoneal dialysate, is small enough to be comfortably worn, and is safe for continuous patient use presents many challenges. The device must be both simple to use and flexible enough to provide effective treatment to a range of patients. It must achieve a wide range of toxin removal goals and still be lightweight.

One of the challenges of the currently available sorbents from SORB Technologies is their small particle size. Using small particles in a column results in a large pressure drop which must be overcome by the pump and battery, which adds to the size and weight of the system. While the sorbents could be supported by a more porous inert matrix, this also adds extra weight and volume. Another solution is to pack the sorbents in the shell space of a hollow fiber dialyzer. Molecules in the lumen fluid can diffuse across the membrane and interact with the sorbent, as in Fig. 1. This would create a fluid path with little flow resistance but also allow the fluid to be exposed to the sorbent.

The size/weight of the current sorbent cartridge could also be reduced by changing the enzyme supporting material. Urease from jack beans could be supported or retained in a number of more efficient ways. Urease could be attached to a support that serves a second purpose such as the hollow fiber membrane or porous sorbent particles that would also adsorb other toxins. Additionally, with appropriate selection of membrane pore size, the enzyme will be retained in the sorbent space without need of supporting material due to size exclusion of the membrane.

One disadvantage of the SORB system is that the sorbents used to regenerate the dialysate adsorb calcium and magnesium from the dialysate, such that these cations must be continuously infused as a replacement fluid. For a wear able system that incorporates these sorbents, this would require an additional pump in the system for re-infusion of calcium and magnesium. Instead, to maintain the device as

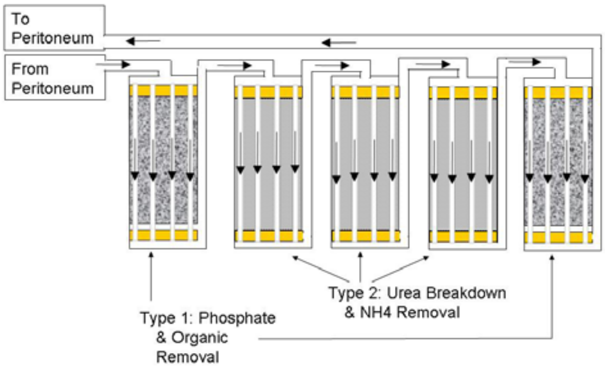

Fig. 1 Example of wearable peritoneal dialysis device

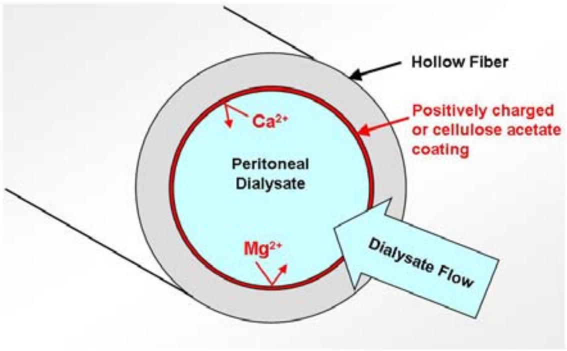

Fig. 2 Example of divalent cation retaining membrane

small as possible, an ion rejecting membrane could be used to retain these cations in the dialysate, as in Fig. 2.

In this case, toxins that are to be removed would be able to permeate the membrane but cations like calcium and magnesium would be rejected. Such a membrane could be achieved by using a cation-rejecting material such as a positively charged material, fatty acids, or other polymers, like cellulose acetate. Furthermore, as demonstrated in Figure 3, if the ion-rejecting membrane also reduces the concentration of sodium exposed to the sorbent, the capacity for adsorbing ammonia will be higher.

Standard HD membranes allow free passage of sodium across the membrane, while reverse osmosis membranes retain virtually all sodium. By depositing an interfacial polymerized coating on a standard dialyzer, it is possible to produce an ion-rejecting membrane which allows passage of urea while retaining sodium. A solution containing urea and sodium was recirculated through the lumen of a coated dialyzer while RO water was pumped countercurrently through the shell side. As shown in Fig. 4, the Na concentration remained constant while the urea concentration fell.

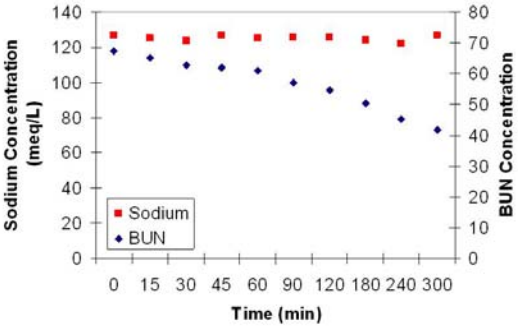

Fig. 4 Sodium rejection by specially-coated dialyzer membrane

The sorbents have been routinely tested for removal of typical toxins, such as urea, phosphate, and creatinine, but testing for removal of toxins that are inadequately removed by regular dialysis treatment, such as β2 microglobulin, or toxins with unknown removal requirements, such as p-cresol sulfate, have not been as thoroughly studied. Recently, a few such experiments have been conducted using sorbents available from SORB Technologies. Fig. 5 shows an adsorption isotherm of β2 microglobulin on the SORB activated carbon. More protein is adsorbed as the fluid concentration increases in the range of 2-15 mg/g. In another set of experiments performed by our colleagues at the Renal Research Institute, dialysate containing p-cresol sulfate was exposed to a current version SORB cartridge and the concentration of p-cresol sulfate at the inlet and outlet of the cartridge was determined, as seen in Fig. 6. This demonstrated that virtually all of the p-cresol sulfate is bound by the sorbents within the cartridge. Because these sorbents are non-specific, these experiments suggest that the sorbents are capable of removing other toxins, but quantitative extrapolation to untested toxins is not possible.

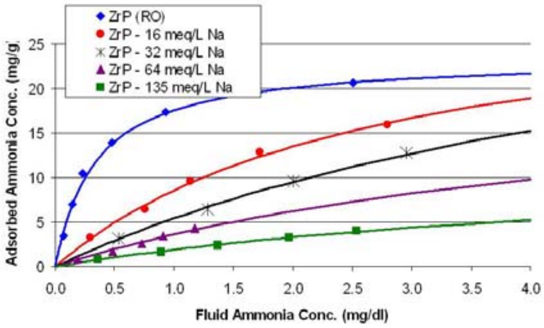

Fig. 3 Ammonia isotherms for ZrP in solutions of sodium chloride

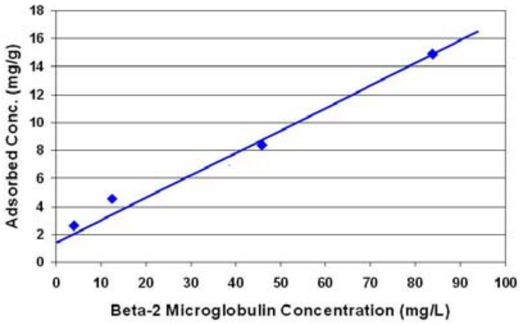

Fig. 5 Beta-2 microglobulin binding isotherm on activated carbon

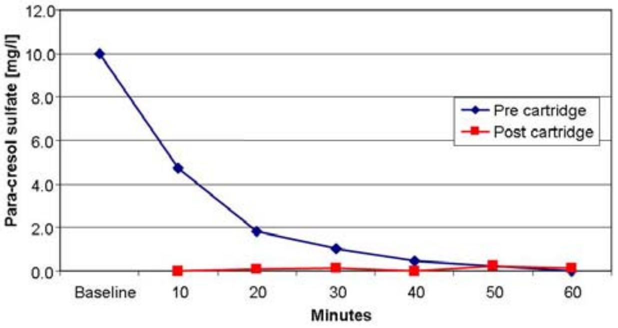

Fig. 6 Removal of p-cresol from PD fluid by SORB cartridge

A prototype of the integrated membrane/sorbent system is shown in Fig. 7 and 8. The flat hollow fiber cartridges have rounded sides for comfort. The combined weight of the cartridges, pump, and batteries is less than 2 kg.

V. CONCLUSIONS

Recently, great strides have been made toward developing a wearable artificial kidney, yet significant engineering challenges still remain in achieving targets for size, weight, effectiveness, and ease of use. Specifically, a design for a PD-based wearable system has been developed that addresses some of these issues, including efficient use of volume/space and effective toxin removal. Further work is necessary to prepare for clinical trials of the system.

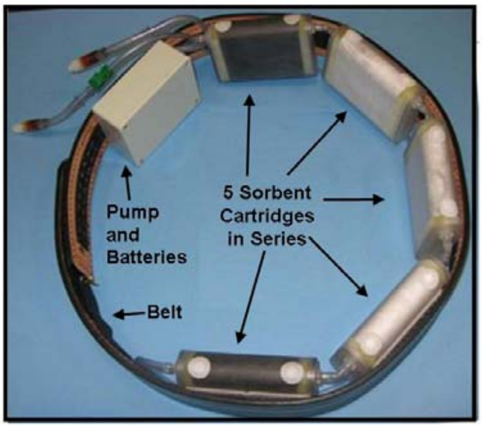

Fig. 7 Prototype wearable kidney belt based on integrated membrane/sorbent approach.

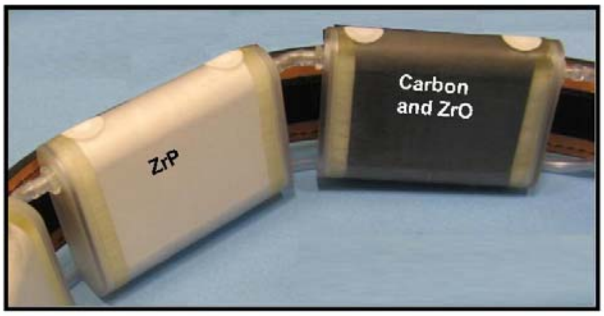

Fig. 8 Close-up of membrane/sorbent modules

ACKNOWLEDGMENT

The authors wish to thank Drs. N. Levin, P. Kotanko, A. Kruse, S. Thijssen (Renal Research Institute, NY) and. Dr. G. Handelman (U Mass Lowell) for the p-cresol data, and to acknowledge Dr. H. Sandford and other Fresenius colleagues for their many contributions to the WAK project.

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