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Creating a wearable artificial kidney: where are we now?

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A wearable and, ultimately, an implantable artificial kidney is a long-held aim in the treatment of patients with end-stage renal disease, provided that it would combine continuous blood purification, preventing the fluctuations in the internal environment associated with hemodialysis, while maintaining a high efficiency for removal of uremic toxins. Sorbent and enzyme technology, allowing for the regeneration of dialysis fluid, have played a vital role in the development of present prototypes, although the development of a low-weight regeneration module as well as safety and control issues still need to be solved. Whereas the first human trials with a wearable device have been successfully conducted, there are still many hurdles to overcome before wearable dialysis can be routinely implemented in dialysis practice. Important in this respect are the absence of a safe continuous blood access system and the risk balance between anticoagulation and clotting and regulatory aspects.

Dialysis is a life-saving treatment which is used in more than 2.5 million patients worldwide. However, current dialysis modalities are still far removed from replacement of the function of normal kidneys. The most important disadvantage of hemodialysis (HD) is its intermittent character, resulting in large fluctuations in the internal environment in contrast to homeostasis achieved by the normal kidney function. Of special importance are the large swings in fluid status, varying between fluid depletion and fluid overload. Peritoneal dialysis (PD) provides more continuous dialysis, but the clearance of uremic toxins is relatively low. Moreover, technique failure rate of this modality is relatively high in the long term, primarily due to damage caused to the peritoneal membrane by the use of high intraperitoneal glucose concentrations needed for osmotic fluid removal.

Long-term survival in dialysis patients is limited, as compared to the general population. Despite a possible survival advantage early after the start of PD therapy, outcomes between thrice-weekly HD and PD do not differ consistently [1]. Evidence, mainly from observational studies, suggests that survival by extended HD (i.e., more frequent or with more hours per treatment) is superior in comparison to conventional HD schedules [2]. In addition, extended HD treatments are associated with other benefits such as improved quality of life, nutritional status and cardiac structure, and a reduced pill burden, at lesser costs as compared to in-center HD treatment. These treatments are preferably performed in the home setting. However, due to various reasons, such as physician attitudes, economic factors, logistics and facility policies, only a relatively small percentage of patients are treated with home HD. Moreover, a disadvantage of extended HD treatments, even when performed in the home setting, is that patients are connected to a large medical device for long periods of time, severely affecting their mobility. The weight of conventional HD modules is usually ≥60 kg. Also, purification of approximately 120 l of water per session (by a separate module) is needed. Moving such devices to other locations, for example, for a holiday, is not a realistic option. Despite important advances toward miniaturization, the smallest HD module currently

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available still has a weight of approximately 35 kg (www.nxstage.com).

Thus, in order to combine efficient toxin clearances with gradual fluid removal, whilst allowing flexibility for the patient, a wearable artificial kidney (WAK) would be a great asset. The concept of a miniature dialysis device is based on continuous regeneration and reuse of a small amount of dialysis fluid in a closed-loop system instead of using large volumes of dialysis fluid in a single pass configuration as done in conventional dialysis. The search for a wearable kidney has a long history and was initiated by Willem Kolff, pioneer of contemporary HD therapy [3]. He developed a wearable kidney unit with a total weight of 3.5 kg, comprising a blood and dialysate circuit with pumps, batteries, tubing and a charcoal regeneration module. The device allowed for continuous removal of water, sodium and some uremic solutes such as creatinine. However, this device could not really be considered wearable as the patients also needed to be connected intermittently to a 20 l dialysate batch to allow for urea and potassium removal [3].

A more advanced regeneration module, based on sorbent and enzyme technology, was proposed in 1986. The sorbent cartridge, used for purification of the recirculated dialysis fluid, included urease for removal of urea, charcoal for adsorption of non-urea organic toxins, zirconium phosphate for removal of potassium and (urease-generated) ammonium, and zirconium oxide for removal of phosphate [4]. This combination of sorbents and urease (the so-called REcirculating DialYsis [REDY] system) also formed the basis for the WAK developed by Davenport *et al*. This device of approximately 5 kg was successfully tested in a first-in-human trial during 4–8 h. Creatinine clearances of around 21 ml/min could be achieved using mean blood and dialysate flow rates of 49 and 56 ml/min, respectively [5].

Whereas (near) continuous and efficient removal of uremic solutes as well as water and salt would be a great asset of wearable devices, one of the major challenges is removal of urea. This is due to the relatively large amount which needs to be removed daily (around 200–400 mmol = 12–24 g), with direct sorption of urea being extremely difficult. There is experimental evidence showing adsorption by carbonyl compounds such as ninhydrin [6]. However, this has not yet found its way into current prototypes for wearable devices, most likely because of the lack of clinical evidence and the need for large sorbent volumes. Present prototypes rely on urease, which catalyzes the hydrolysis of urea to bicarbonate and ammonium. In the second step, ammonium, which is more toxic than urea, is adsorbed by zirconium phosphate [5]. Although high urea removal rates can be achieved with small amounts of immobilized urease [7], a large amount of zirconium phosphate (>1 kg/day) is required to remove the generated ammonium, which limits further miniaturization.

Next to direct sorption and urease, another possibility for urea removal is electro-oxidation, which converts urea directly into CO_2 and N_2. Advantage of this approach is the fact that there is no risk for saturation of a sorbent, and that urea removal can be regulated by adjusting the current over the electrodes. This approach was found to be effective in an *in vitro* setting. A drawback of electro-oxidation is the oxidation of chloride leading to the formation of reactive chlorine species, such as chloramines, which have to be removed by activated carbon downstream from the electrodes [8]. The prototype (Nephron+) which is based on this approach currently has a weight of around 3 kg.

Besides urea, which is probably only toxic when systemic levels are persistently high, other uremic toxins such as middle molecules and protein-bound toxins deserve attention. It has been shown by Gura *et al.* that adequate removal of phosphate and 'middle molecules' like beta-2 microglobulin can be achieved by the WAK, provided that it is operated continuously [9]. A limiting factor for the removal of protein-bound uremic toxins is the fact that only the free fraction can pass dialysis membranes. So-called 'mixed matrix membranes' consisting of an outer layer with activated carbon particles and a porous particle-free hemocompatible inner membrane, combining adsorption and diffusion in one step, may considerably improve protein-bound toxin removal and could become an important asset for wearable devices in the future [10].

An important point of consideration is the influence of the ion-exchange sorbents on the electrolyte mass and acid–base balance. Cation-exchange sorbents, such as zirconium phosphate used in the REDY system, also adsorb calcium and magnesium. A negative magnesium and calcium balance can be prevented by post-cartridge supplementation, as applied in the REDY system, or by preloading of the sorbents [11]. The adsorbed cations are partly exchanged for sodium and hydrogen ions, which may induce a positive sodium balance (complicating body fluid and blood pressure regulation) and (an increase of) metabolic acidosis, respectively. This issue is particularly relevant for the REDY system where large amounts of urease-generated ammonium (~0.4–0.8 mole per day) are adsorbed [12]. To prevent sodium release, a hypotonic dialysate reservoir downstream of the sorbent cartridge is applied in the REDY system resulting in initial dialysate sodium concentrations lower than the patient's plasma level and final dialysate sodium concentrations (at the end of the treatment) higher than the patient's level. Metabolic acidosis is prevented by addition of (sodium) bicarbonate to the reservoir which can be adjusted to the patient's bicarbonate level and the estimated amount of urea that is exchanged for hydrogen [12]. Considering the high risk of electrolyte and acid–base disturbances, adequate monitoring by miniaturized sensor technology in dialysate affluent and effluent would be important.

There are still major bottlenecks with regard to the direct access to the bloodstream with wearable devices, such as the risk of considerable blood loss and air embolism in case of accidental disconnection. Negative intravascular pressure in a prone position may hamper the supply of blood to the HD device when using a central venous catheter. The use of 'single needle' applications, needle ports with check valve systems, subcutaneous access devices and safety measures within the device itself may circumvent some of these problems [13,14]. These problems can be partly circumvented by the use of a portable instead of a wearable device, which would allow for more flexibility for

the patient (e.g., no adjustments for the home situations would be necessary and easy transport outside home would be possible without the need for tap water access). On the other hand, such a device cannot be considered really 'wearable'. Developments toward a portable dialysis device, based on the collaboration between the Dutch Kidney Foundation and AWAK-Debiotech, are ongoing [15]. Besides access, the balance between anticoagulation and clotting risk, as well as the safety and control features of wearable or portable devices all require careful consideration [5,13,14]. This also holds true for costs and reimbursement, as well as regulatory aspects.

Wearable devices with sorbent systems can also be used to enhance the efficacy of PD. Since PD is a blood-free dialysis technique, not requiring a vascular access, a wearable device for PD may be within closer reach than that for HD [14]. Considerable improvement in PD efficacy can be achieved by continuously regenerating the peritoneal dialysate, thereby maintaining a large plasma–dialysate concentration gradient. This might allow reduction in the number of (time-consuming) exchanges, while still improving toxin clearance. By continuous flow PD, the urea clearance (normally about 6–8 ml/min with four to six 2 l exchanges per day) could be augmented to well above 30 ml/min using recirculation flow (200–300 ml/min) and two peritoneal catheters [16]. A wearable PD device may also prolong technique survival. Reduction in the number of exchanges and (dis)connections of the PD catheter decreases the risk of contamination and may lower peritonitis rates. In addition, continuous glucose infusion by a wearable PD device may reduce functional deterioration of the peritoneal membrane by avoiding very high toxic glucose concentrations needed for osmotic fluid removal in conventional PD. Conceptual proposals for wearable PD (ViWak PD) were launched in the previous decade [17]. Practical developments toward a wearable continuous peritoneal device are ongoing [15], but have not yet entered clinical trials.

In the ideal situation, dialysis should be performed by an implantable device. However, despite recent advances, this is still far removed, predominantly due to biocompatibility issues. A recent experimental study, however, showed remarkable biocompatibility of polyethylene glycol coated silicon membranes. This membrane could serve as the scaffold for an implantable renal assist device. The underlying principle is that silicon nanopore membrane would allow for a filtration rate of 30 ml/min, whereas a connected bioreactor with renal tubular cells on a silicon nanopore platform would allow for selective reabsorption of water and electrolytes [18]. Developments in this area are still preliminary but exciting, and will likely coincide with advances in kidney regeneration and tissue reengineering [19], although important challenges in terms of biocompatibility, immunogenicity, cell viability and effectiveness remain [20]. As an intermediate step, a wearable PD device, with a combination of sorbents and a scaffold with renal epithelial cells has been proposed (Bioartificial Renal Epithelial Cell System) [21], in order to improve the metabolic and immunomodulatory effects of dialysis treatment [18].

To conclude, there are important advances in the development of a WAK, involving an intriguing combination of established and future technologies. However, there are still substantial technical challenges, with regard to safety, operation of the device and effectiveness, which need to be overcome. An important dilemma remains whether patients will accept to wear a device every day for an extended period of time. Possibly, a portable device for intermittent HD, which can be easily carried by the patient and used at his or her discretion without the need for water supply, or a PD-based device allowing for higher efficacy by recirculation of regenerated fluid at night would pose a viable alternative in the near future.

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