The Current and Future of Bioartificial Kidney and Wearable Dialysis Device

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INTRODUCTION

The applications of new disciplines such as miniaturization, microfluidics, and nanotechnology to the field of artificial kidney are leading to a new era of dialysis devices with transportability and wearability. Recent effort for the past 10 years has made it feasible to replicate the differentiated absorptive, metabolic, and endocrine functions of renal tubular cells, which was integrated into the filtration function of current dialysis, so called bioartificial kidney mimicking functional nephron. In addition, other innovative groups are currently focusing on application of micro- and nanometer scale engineering to the manufacture of highly efficient membranes that is ultimately implantable into human body.

In this review, recent efforts in the development wearable dialysis devices, bioartificial kidney and implantable novel membrane are presented, with a review of the challenges remaining in implementation of this technology.

WERABLE DIALYSIS SYSTEMS

1. The early year's efforts for portable dialysis

The earliest efforts to make the portable dialysis devices date back to Gordon's sorbent cartridge system [1] in the late 1960s (Fig. 1) and Kolff's wearable artificial kidney system[2] regenerating spent ultrafiltrate as dialysate in the early 1970s (Fig. 2). The first portable dialysis devices were based a batch dialysate system, with the spent dialysate regenerated by a charcoal module, coupled with rechargeable batteries.

Despite the enthusiasm for portable hemodialysis, these devices were abandoned due to the technical limitations of those days in reducing size and weight. However, the interest in sorbents led to the development of commercially available sorbent-based dialysis called REDY or Sorbsystem and many wearable artificial kidney systems have been choosing to use sorbent cartridge to regenerate dialysate, later on.

2. Peritoneal dialysis (PD)-based wearable dialysis device

Basically PD is a kind of wearable and portable form of dialysis in that it provides a continuous renal replacement therapy with well tolerated fluid removal and smooth correction of uremic abnormalities.[3] Taking advantage of properties, Ronco and colleagues[4] have proposed a wearable continuous PD system, so called "The Vicenza Wearable Artificial Kidney for Peritoneal Dialysis (ViWAK PD)" model. The model

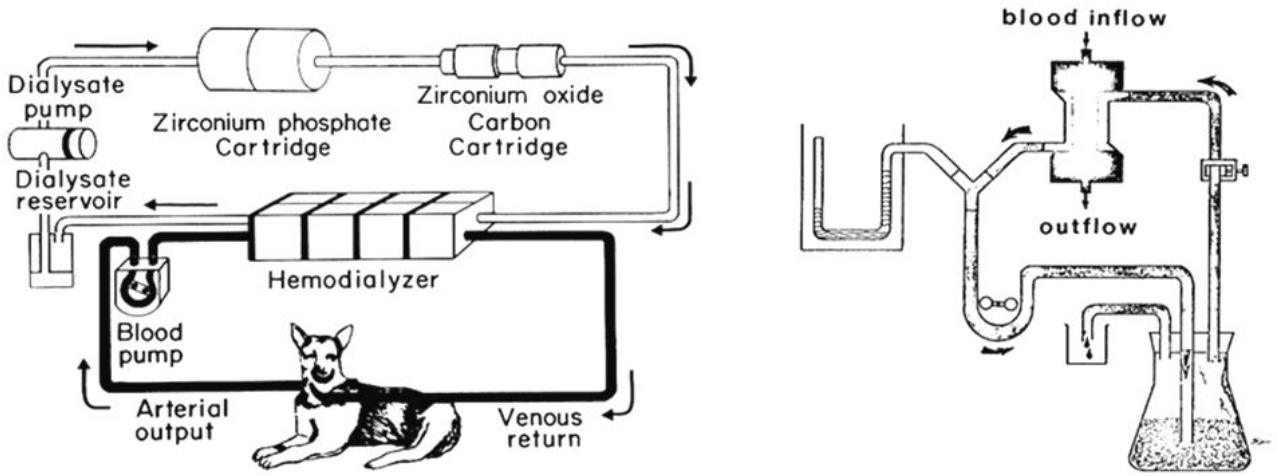

Fig. 1. Portable dialysis devices in the early years (a) Sorbent based low volume recirculating dialysate system. (from Gordon A et al. Trans Am Soc Artif Intern Organs, 1969). (b) Continuous arterio-venous hemofiltration in a wearable device (from Dharnidharka SG and Kolff WJ et al. Trans Amer Soc Artif Intern Organs, 1973)

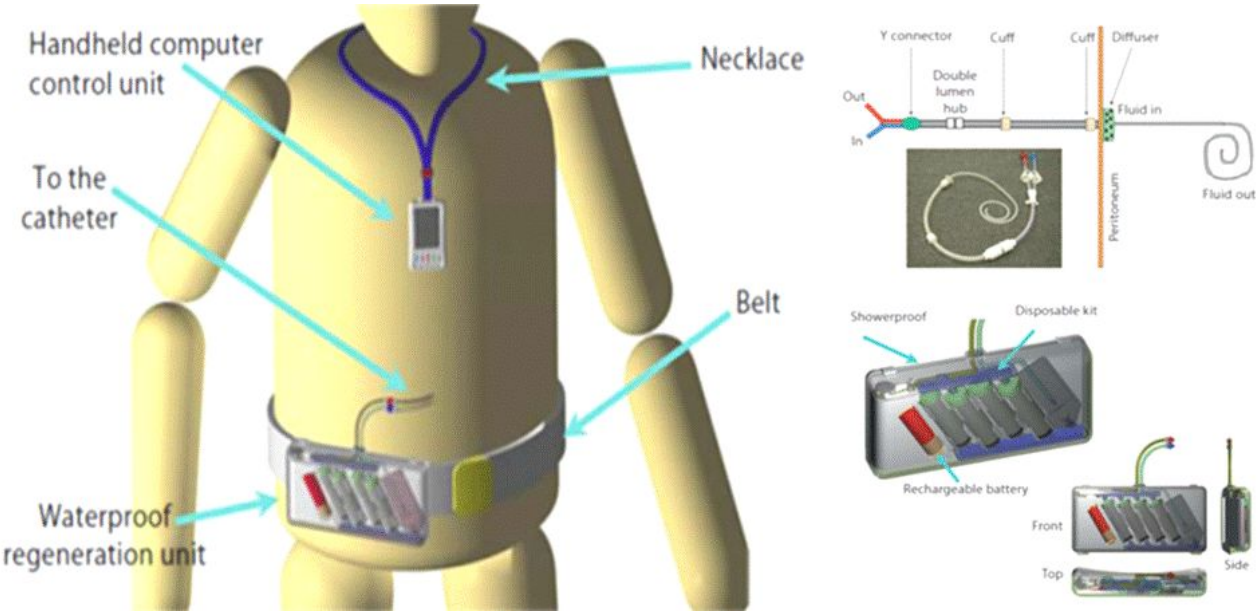

Fig. 2. Prototype of a wearable continuous peritoneal dialysis device suggested by Ronco and colleagues. (from Ronco C et al Blood Purif, 2007)

consists of dialysate lines with peritoneal catheter, a miniaturized rotary pump, a circuit for dialysate regeneration, and a handheld computer as a remote control.

This system has been tested still only in the experimental condition using exhausted PD solution. The system operates 24 h/day circulating 12 liters of exhausted PD solution at a rate of 20 ml/min and provides creatinine and β2-MG clearance in the range of 15-16 liters/day, corresponding to a weekly clearance of 100-110 liters. Problems remain to be solved in the present configuration including the addition of an injection system for glucose and bicarbonate, a system to reduce fibrin delivery to the sorbent, and a complex sorbent system to make sure a complete removal of small molecules including urea.

3. HD (Hemodialysis)-based wearable dialysis device

Gura and colleagues[5] have published research into a light-weight, wearable, continuous ambulatory ultrafiltration device consisting of a hollow fiber hemofilter, a battery-operated pulsatile pump, and two micropumps to control heparin administration and ultrafiltration. The device used a commercially available 0.6 m^2 polysulfone high flux dialyser. A pulsatile blood pump was specially designed, powered by a standard 9-V battery, pumped the blood and dialysate in a countercurrent direction. The device regenerates dialysate with small device similar to the once commercially-available REDY dialysis system. The total weight of the device was about 5 kg.

Although Phase 1 and phase 2 trials have been undertaken with this hemodialysis device, these have typically been short term. It need accumulated experience before these devices can truly be introduced into every day clinical practice[6, 7].

BIOARTIFICIAL KIDNEYS

1. Renal tubule cell assistance device (RAD) and the first bioartificial kidney

The kidney's roles in metabolic, endocrinologic, immunologic regulation are not addressed by current dialysis technologies. In contrast to wearable dialysis systems focusing on wearablity, bioartificial kidney

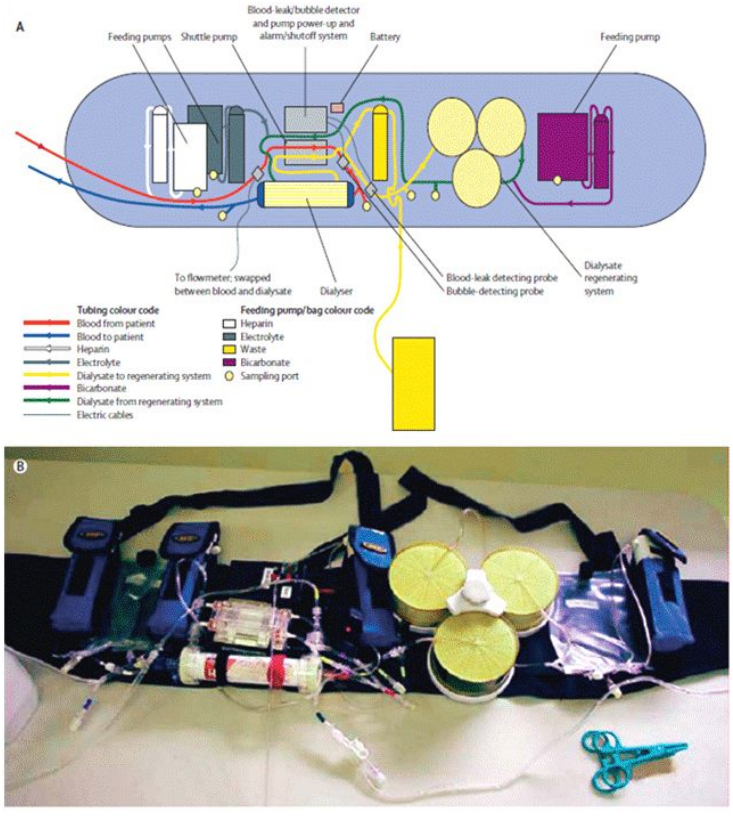

Fig. 3. A wearable haemodialysis device fabricated by and colleagues. (from Davenport A and Gura V et al. Lancet, 2007)

focuses on the integration of renal tubule cell into filtration functions of dialysis.

The first RAD was developed by Humes and colleagues at the University of Michigan in 1997. It contained more than 109 renal tubule cells using a standard hemofiltration cartridge. The RAD was incorporated into extracorporeal circulation system in series by a conventional hemofilter with structural construction of circuit mimicking functional nephron. This strategy allows the bioartificial kidney to replicate the structural and metabolic, endocrinologic, immunologic function of the nephron (Fig. 4)[8, 9]. The first bioartificial kidney was successfully tested with uremic dogs with bilateral nephrectomies[10].

2. Clinical results of bioartificial kidney

The first human clinical study was carried out in 10 critically-ill patients with acute kidney injury (AKI). RAD demonstrated differentiated metabolic and endocrinologic activity in the patients. It maintained stably and safely up to 24 hour showing cardiovascular stability and increased native renal function. Six of the 10 treated patients survived past 30 days, with mortality reduced to 40%. These favorable Phase I/II trial results led to a randomized, controlled, open-label Phase II trial conducted at 12 clinical sites in the U.S[12]. Treatment with bioartificial kidney for up to 72 h promoted a statistically significant survival advantage over 180 d of follow-up in ICU patients with AKI showing an acceptable safety profile.

INNOVATIVE NOVEL IMPLANTABLE MEMBRANE

In parallel with progress in wearable dialysis devices and bioartificial kidney, considerable interest is emerging in novel technologies to overcome the barriers to implantation of existing membranes. Current hollow fiber polymer membranes are not suitable for implantation because the pores typically have a broad size distribution and irregular features. Besides the matter of size, these features also result in low hydraulic permeability and thus mechanical pumps are needed to move blood through the filter. Engineering narrower pore-size distributions can ameliorate this dilemma, allowing sharper transitions from passage to retention and maximizing mean pore size[13, 14].

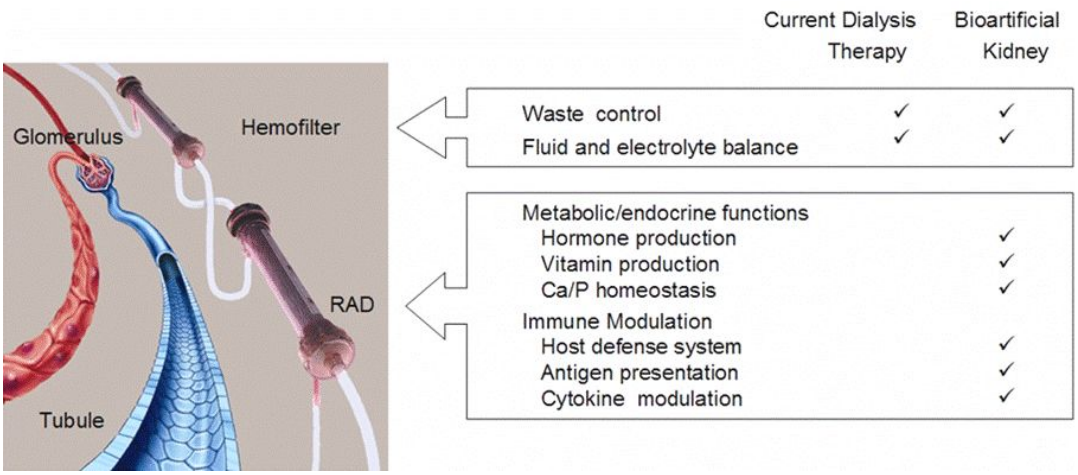

Fig. 4. The basic concept of bioartificial kidney to integrate differentiated absorptive, metabolic, and endocrine functions of renal tubular cells into the filtration function of current dialysis technologies. (from Song JH and Humes HD et al. Semin Dial 22:603-9, 2009)

1. Nanofabrication of Silicon Nanopore Membrane (SNP)

Fissell and colleagues are developing a nanopore membrane to replace the filtration function of the glomerulus without the hemofilters and mechanical pumps. It has been prototyped from silicon substrates using an innovative process based on microelectromechanical systems (MEMS) technology, which refer to the study of devices and features at the cellular and molecular length scales.

Prototype SNP were manufactured with highly uniform smooth-walled "slit-like" pores mimicking natural glomerulus with pore size controlled within 1 nm (Fig. 5). Extensive testing of the transport properties of this novel biomimetic membrane is underway. Recent data provide encouragement that protein permselectivity is feasible with this technology, paving the way for a glomerular analog with high hydraulic permeability and strict size and charge-dependent rejection of solutes.

2. Membranes as a scaffolding for cell growth: Living membranes

Following the introduction of SNP, attention was directed toward exploring these materials as scaffolding for renal cell growth as implantable bioreactor[15]. The development of such living membranes incorporating renal tubule cells will replace the reclamation, metabolic, and endocrine functions of the kidney.

On the other hand, microfabricated capillary networks with MEMS techniques and endothelial attachment and growth have made substantive advances recently[15]. Protein deposition on the membrane and thrombotic occlusion of the hollow fibers reduce the durability of the filtration membrane. The use of autologous circulating endothelial cell progenitors provides a histocompatible cell source for device fabrication. The clinical development of this approach is still years from application.

3. Human nephron filter

There are several other novel approaches to overcoming current membrane limitations using nanotechnology. Nanotechnology refers to atomically precise functional machine systems developed on the scale of

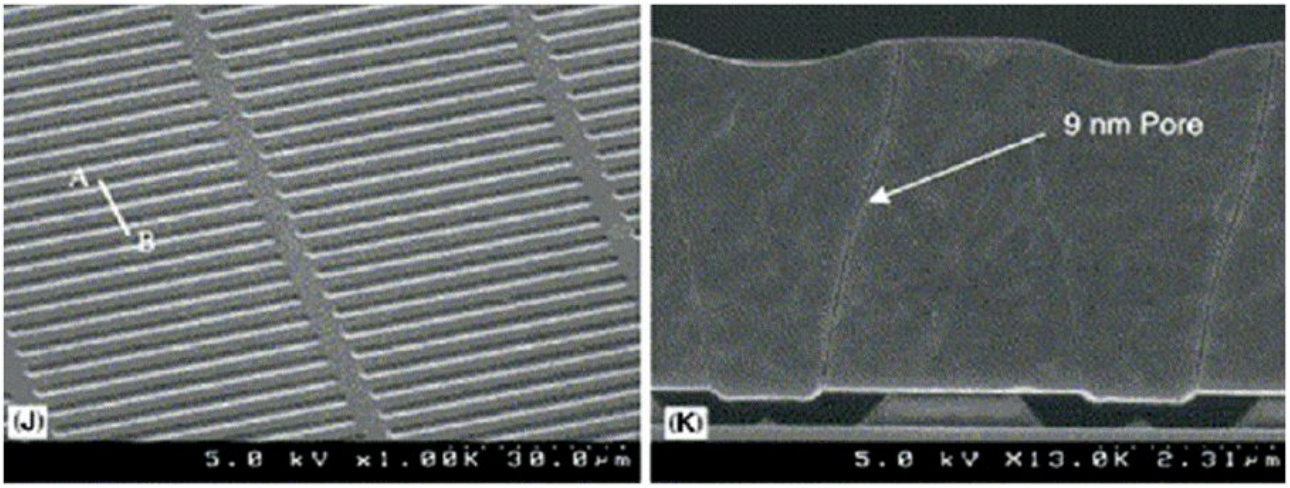

Fig. 5. Scanning electron micrograph images of a protoype silicon nanopore membrane (from Fissell WH and Humes HD et al. Transl Res, 2007)

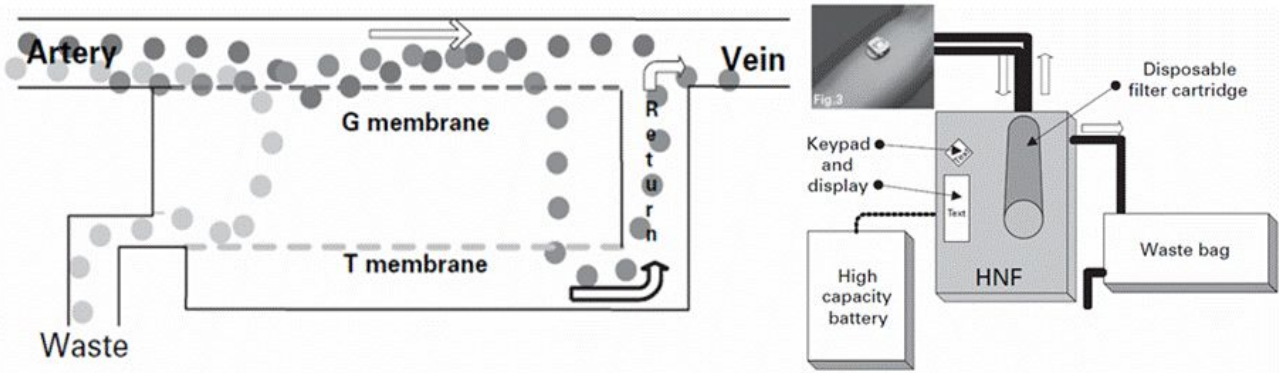

Fig. 6. The concept of human nephron filter and its wearable system. (from Nissenson AR: et al. Semin Dial, 2009)

the nanometer (one billionth of a meter: 1 nm=1/1,000,000,000 m). Some examples of nanoscale application to dialysis membrane are already appearing, the first the recent introduction by Fresenius Medical Care of the Helixone® membrane[16].

Nissenson et al.[17] have currently proposed the concept of a two-stage renal replacement device, termed the "human nephron filter (HNF)," comprising a "G membrane" and "T membrane" (Fig. 6). The glomerular (G) membrane is a conventional hemofiltration membrane that passes small solutes and retains macromolecules and cells. The tubular (T) membrane is a synthetic membrane incorporating synthetic ion and aquaporin channels. The T membrane in theory allows reabsorption of salt and water while other solutes are progressively concentrated in the ultrafiltrate stream.

The HNF has been computer-modeled and operating 12 hr per day, 7 days per week. It is estimated that the HNF provides the equivalent of 30 mL/min glomerular filtration rate. Although only numerical simulations have yet been performed, the "HNF" concept is exciting as it presents the possibility of dialysis-free renal replacement. Animal studies is planned to begin in the next couple of years.

CONCLUSION

The next-generation dialysis devices should be wearable or implantable system capable of performing continuously and possibly replacing all functions of normal healthy kidney. The effort to achieve such devices need multidisciplinary approaches involving stem cell, bioengineering, and nanotechnology research. The advent of miniaturized pump systems, microengineering, and sorbent-based regeneration technology will make it feasible to develop a more compact, long-lasting, portable/wearable kidney. Nanofabrication of novel membranes could overcome the limitations of existing membranes, which cannot be implanted without pumps, and enable a paradigm shift in renal replacement treatment.

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