WEARABLE ARTIFICIAL KIDNEY – EVOLUTION OF ITS CONCEPTS AND CURRENT STATE-OF-THE-ART

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Abstract

Shortly after intermittent haemodialysis became established treatment of chronic renal failure, the first wearable artificial kidney (WAK) device projected or even constructed to solve the problem of intermittent treatment unphysiology. Successful development of hollow fibres enabled construction of a sufficiently small dialyzer to be worn and recirculation of dialysate through a sorbent cartridge lead to tremendous drop in dialysate volumes needed. Tested were WAK devices based both on haemodialysis (HD) or on haemofiltration (HF) (after highly permeable membranes became available) as well as on peritoneal dialysis (PD). Later, some other techniques and processes appeared in armamentarium of WAK designers, such as charged membranes, electrodialysis, nanotechnological processes enabling to create membranes with solute-specific pores. Also a few hybride constructions appeared during the last decade using membranes coated with tubular epithelial cells to mimic tubular resorption of biological kidney. With current trends towards more frequent HD with higher material costs, WAK effort got another impetus, this time purely economical. The first commercially available WAK (although still waiting for a CE mark in Europe and FDA clearing in USA) was developed by a Singaporean company AWAK Technologies in 2011. A European WAK is being developed as a joint project in frame of FP7 and is expected to be ready by 2014. However, acceptance of WAK instead of conventional intermittent therapy both by physicians and by the patients themselves still remains unresolved.

Keywords

Wearable artificial kidney, haemodialysis, peritoneal dialysis, sorption, bioartificial device

Introduction

The kidney was the first organ function of which was successfully replaced by an artificial technical device on long term. Haemodialysis (HD)-based artificial kidney was however by no means perfect. Nephron, the principal functional unit of biological kidney, is a two-stage system. The first one – glomerulus – produces so called primary urine (in fact plasma filtrate) by filtration. The second one – tubulus – ensures resorption of all solutes needed in the organism and only true waste leaves kidney in final urine. HD has replaced this two-stage system by just single-stage process – diffusion and filtration across the dialyzer membrane. However, diffusion efficiency quickly decreases with increasing molecular weight of the diffusing solute while filtration in glomeruli excretes all solutes in the same rate irrespective of their molecular weight. Although with the introduction of convective techniques such as haemodiafiltration (HDF) or haemofiltration (HF) solute removal has got much closer to biological kidney function, the second principal difference of artificial kidney from its biological counterpart – intermittent character of its application – remained preserved. Most patients dialyse thrice weekly for 3 to 5 hours while biological kidney works 24 hours a day, 7 days a week. Direct consequence of that imperfect substitute is an unphysiologically high cyclic variation in many biochemical parameters as well as in hydration. Carl Kjellstrand even considered this unphysiology the main cause of dialysis side effects already in mid-seventies (1). Inspired by the Kjellstrand´s work, a mathematical theory was developed at Prague-Strahov dialysis department (2). It was based on a plot with blood urea time-averaged concentration (TAC) on X-axis and its time-averaged deviation (TAD) on Y-axis and

clearly showed how far the different then existing dialysis techniques were from "normal" healthy situation with continuous kidney function (see Fig. 1). Yet continuous application of then stationary artificial kidney would mean to immobilize the patient. To solve this problem, wearable (WAK) or even implantable artificial kidney appeared to be the right concept.

Key pre-requisites of WAK and evolution of its concepts

There were two main obstacles to converting an HD device of the sixties or seventies into a WAK – too big dialyzer to be worn and the large amount of

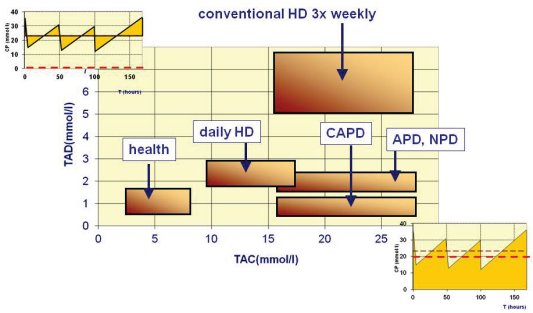


Fig. 1: The TAC/TAD concept to assess dialysis adequacy: TAC (plasma urea time-average concentration) shows the weekly mean around which the actual concentration fluctuates, TAD (plasma urea time-averaged deviation) shows mean fluctuation around the TAC value and serves as a marker of physiology of a certain treatment method or schedule; dashed line on small plots at the axes with weekly plasma urea (CP) profile define the TAC and TAD; (CAPD stands for continuous ambulatory peritoneal dialysis, APD for automated peritoneal dialysis, and NPD for night peritoneal dialysis)

dialysate needed for an efficient HD. However, pre-requisites to solve both problems appeared relatively early in HD history: Capillary dialyzer developed in the sixties had low blood volume and possessed apparently sufficient potential for further miniaturisation and the works of Yatzidis (3) on adsorption of uraemic toxins on charcoal suggested that sorption could do away with the large amounts of dialysis fluid. It did not go unnoticed. Already two years later Blaney suggested use of adsorption on charcoal in WAK (4). However, a serious problem was detected – insufficient affinity of charcoal to urea, the most abundant waste metabolite. It was first shown by Dharnidharka (5) from Kolff´s group – while concentration of urea and creatinine was brought close to zero by circulation of blood via charcoal, drop in urea concentration was much less pronounced. The patented idea of Blackshear to cool the charcoal cartridge down close to 0°C where its affinity to urea sharply increases (6) has proved rather impractical. The idea of Gordon to convert electroneutral molecules of urea in ammonium ions by means of the enzyme urease (7) and remove those ions by a suitable ion-exchanger appeared much more viable. Based on this idea, the first truly portable HD system REDY was then built by a Dutch company Organon Teknika – Fig. 2. It worked with only five litres of dialysate which recirculated via a sorption cartridge containing charcoal, urease layer and zirconium phosphate. The issue of calcium and magnesium ions removal together with ammonium was solved by slow continuous infusion of calcium and magnesium chloride into dialysate during HD. The REDY cartridge subsequently became a favourite component of many WAK constructions throughout the seventies and eighties.

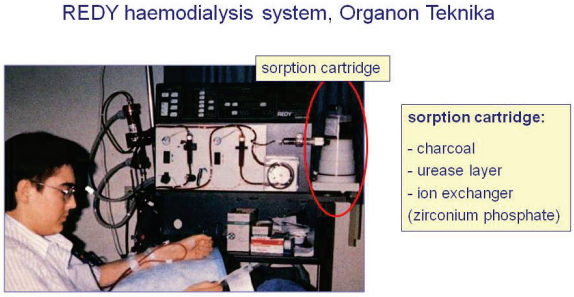


Fig. 2: Haemodialysis system REDY manufactured in the seventies and eighties by Organon Teknika, NL; dialysate volume needed per dialysis: 5 litres; composition of the disposable sorbent cartridge: charcoal (to remove waste metabolites except urea), urease layer (to convert urea into ammonium ions), ion exchanger (to remove the ammonium ions), (http://www.advancedrenaleducation.com/sorbentte chnology/)

The seventies were a very fruitful era in WAK construction efforts. Probably the most active was

the team of dr. Kolff in Salt Lake City, Utah. They developed both peritoneal dialysis (PD) and HD-based WAK using a capillary dialyzer and charcoal or later the REDY cartridge – Fig. 3 a, b (8).

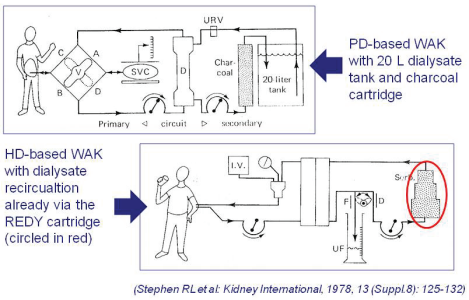


Fig. 3: different WAK constructions from the Kolff´s group in the seventies:
Upper picture – PD-based WAK with a secondary dialyzer circuit to clean peritoneal dialysate partly by diffusion against dialysate in the tank and partly by sorption on charcoal
Bottom picture – HD-based WAK with the REDY sorbent cartridge in dialysate circuit.

But different WAK projects were running in a few other countries, too. Henne in Wuppertal, Germany, used a dialyzer with surface area of 0,1 m^2 and just one litre of dialysate which was changed every two hours. However, he did not use any sorption cartridge but added sorbent powder directly into dialysate (9). In the end of the seventies, theory of middle molecules uraemic toxins emerged and use of more porous membrane started to be endorsed. It affected also the WAK field. Otuba constructed his WAK in Tokyo as a double stage device, combining a plasmafilter and sorption cartridge in the first stage followed by a high-flux ultrafilter (10) and tested it with dogs. An entirely novel approach was tested by Neff – a haemofilter connected to a Scribner shunt (i.e. without a blood pump) generated about 0,5 litre of filtrate per hour, but instead of regenerating it with a usual sorption cartridge he discarded all the filtrate and provided the patients with orally administered substitution fluid (11). Four-days of reported *in vivo* use did not result in any diarhea or any other gastrointestinal problems.

With establishment of sufficient dialysis infrastructure able to cover dialysis needs in developed countries in the eighties, work on WAK lost a lot of its momentum. Yet one achievement must be mentioned from that period: Using conventional continuous arterio-venous haemofiltration with filtrate processed via a sorption cartridge, A. Murisasco treated one patient for 1 month and another one even for three month (12) – a record not outdone since then! In the early nineties, an idea of using charged membrane to separate removal of urea from removal of other waste metabolites came from Japan. Tada´s haemofiltration (HF)-based device (13) is depicted on Fig. 4: Filtrate obtained in the first haemofilter

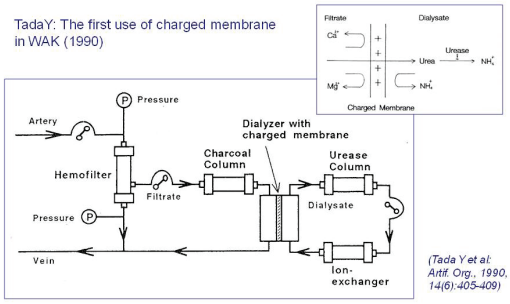


Fig. 4: Haemofiltration-based WAK of Tada and co-workers (Tokyo, 1990): Primary circuit – generation of filtrate in a conventional haemofilter; Secondary circuit – recirculation of filtrate via charcoal and a special dialyzer with highly positively charged membrane allowing diffusional passage of only electroneutral solutes (urea) to the Tertiary circuit – low volume dialysate recirculation via urease (conversion of urea into ammonium aions) and an ion-exchanger (removal of ammonium ions).

recirculated via secondary circuit with a pure charcoal where most waste metabolites except for urea were removed. In series with the charcoal cartridge was a special dialyzer with highly positively charged membrane. That charge effectively blocked diffusion of any cations (Ca^{2+}, Mg^{2+} etc.) but allowed unrestricted diffusion of urea into a tertiary circuit with urease and ion-exchanger for ammonium ions removal. It is interesting to note, that according to the 2010 annual report also Fresenius company, currently number one among dialysis manufacturers, did some WAK-related experiments using charged membranes.

Research and development in WAK field after 2000

With the introduction of highly porous membranes and convective techniques, the conventional thrice weekly treatment has reached a sort of its limit and further improvement is likely to result from introduction of more physiological regimens. In 2004, the International Quotidian Dialysis Registry was started to prove that more frequent and thus more physiological schedules are the right way ahead in renal replacement therapy (RRT). It currently registers some 5000 patients

worldwide and reported treatment outcomes are impressive (14). However, as the material costs for quotidian HD are apparently higher than for conventional 3x weekly HD (5-7 dialyzers and blood lines are needed instead of 3), WAK with its expected device exchanges and/or checks once weekly or even bi-weekly gained a new impetus, this time purely economical. It is the "belt" WAK of V. Gura from United States which has gained the widest publicity during the last decade - Fig. 5,

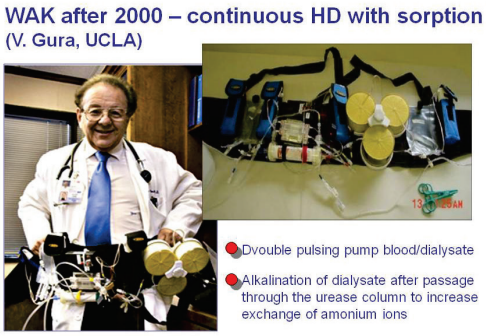


Fig. 5: "Belt" WAK of V. Gura: continuous haemodialysis combined with already "classical" sorption in the dialysate circuit (charcoal, urease, ion-exchanger), novel is the double pulsing pump driving both blood and dialysate and alkalisation of dialysate after passage through the urease to increase efficacy of ammonium ions removal on the ion-exchanger (www.today.ucla.edu/portalut/ 080220_wearable-kidney.aspx).

although except for the pulsing double blood/dialysate pump which increases efficiency and makes the device less prone to clotting it is a rather conventional arrangement (15). Ronco´s group in Vicenza builds their ViWAK (abbreviation of Vicenza WAK) on a PD principle (Fig. 6).

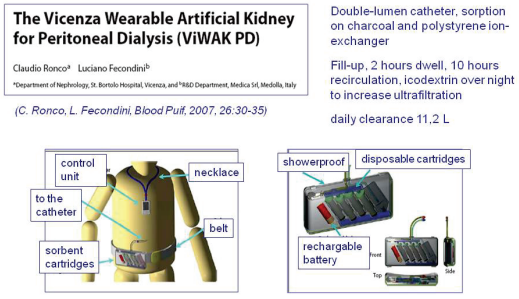


Fig. 6: PD-based WAK of the Vicenza group (ViWAK): belt showerproof construction; daily treatment cycle: fill-in, 2 hours dwell time followed by 10 hours recirculation via double-lumen catheter and disposable sorbent cartridges, use of icodextrin over night to ensure sufficient fluid removal (http://content.karger.com/ProdukteDB/produkte.asp?Aktion=ShowPDF&ArtikelNr=107775&Ausgabe=233672&ProduktNr=223997&filename=107775.pdf).

Peritoneal dialysis solution circulates via a double lumen PD catheter through a battery of sorbent cartridges and daily clearance of urea is assumed to reach about 11 litres (16). Concurrently, they work on a continuous wearable purely ultrafiltration device (WUF) intended for cardiac patients with fluid overload resistant to diuretics (17). Its first "belt" version clearly bespeaks co-operation with Victor Gura but the projected "vest-like" innovation already shows elegance of the "Ital-design" - Fig. 7.

Fig. 7: The continuous ultrafiltration device from the Vicenza group of C. Ronco (left picture - the first version of the device, right picture – vest-contained WUF intended primarily for cardiac patients), (Ronco C et al: Nefrologia, 2011, 31(1):9-16; http://www.revistanefrologia.com)

Considered is also use of this device in HD patients during the interdialytic period - it could eliminate the need for high ultrafiltration rates during HD, responsible for most episodes of intradialytic hypotensions. However, this idea is by no means new, it has been suggested by Shaldon already at the beginning of the eighties (18) but developmental priorities in dialysis field at that time were different. How interesting the concept is becomes obvious from recent findings of Bleyer (19) on significantly higher mortality from cardiovascular reasons on the last day of the longest interdialytic interval (usually three days on thrice weekly HD schedule Monday-Wednesday-Friday) when patient´s overhydration reaches its maximum.

Growing interest in WAK is documented also by the first "World conference on portable-wearable systems for dialysis and ultrafiltration" held in Vicenza in 2010. Although it did not bring any break-through concepts, it provided very good overview of current state of the art in the WAK field. Noteworthy was the presentation of Harashima (20) who presented a system mimicking

tubular concentrating function by combination of electrodialysis, dialysis and filtration. The device was able to increase urea concentration in the test solution 2 to 3 times. Information was also provided on the European project "Nephron Plus" (21). This joint project of ten subjects (industry, universities, renal foundations) from six different European countries with total budget of about 6 mil. Euro, of which over 4 mil. are to be provided by EU within the FP7, should result in an European WAK by 2014.

In 2011, the first WAK to be commercially available was introduced by a Singapore company AWAK Technologies at the ERA/EDTA Congress in Prague - Fig. 8. It is a PD-based device similar to

Fig. 8: PD-based WAK of AWAK Technologies, Singapore – the first WAK to be commercialized (Europe - CE mark still needed, US – FD clearance needed), (www.awak.com/wearable_dialysis).

the Vicenza ViWAK construction. With daily running time of 19-21 hours, 2 to 3 exchanges of the sorbent cartridge are needed (22). Interesting is the fact that AWAK Technologies has utilised a rather old patent of Roberts and Lee from 1993(!)

Recently, some new technologies potentially applicable in WAK have been developed. Magnetically assisted dialysis uses ferromagnetic nanoparticles covered with a sorbent (23). They are infused in the extracorporeal circuit, where the sorbent binds waste metabolites, and are again removed in a magnetic separator before returning the blood in vascular system.

Because the particles diameter is only 30 nm, i.e. 200 times smaller than erythrocyte, their infusion directly in vascular system with an implanted magnetic separator, i.e. without the need to create an extracorporeal circuit, may prove feasible in future.

Another promising direction is application of nanotechnological processes in membrane manufacture. It should enable to create membranes with solute-specific pores which would allow passage of only selected waste metabolites or only solutes to be resorbed from primary filtrate. The latter variant is used in Nissenson project of WAK (24) – Fig. 9. It combines solute unspecific filtration via a conventional high-flux membrane and subsequent filtration of the filtrate across a nanotechnologically manufactured membrane permeable only for solutes to be retained in the body. The secondary filtrate with those substances would then be returned to blood (mimicking tubular resorption) while the remaining waste solutes not able to pass through the membrane would be discarded (mimicking final urine in biological kidney).

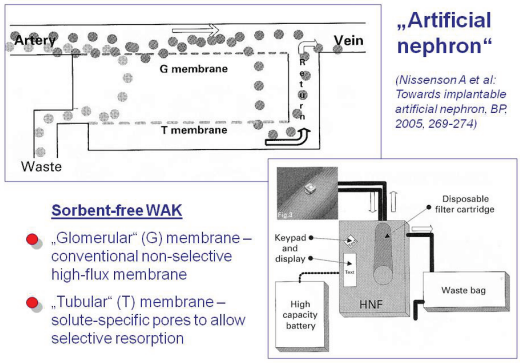


Fig. 9: Sorbent-free WAK (Artificial nephron) of Nissenson and co-workers: "Glomerular" stage realized by a conventional solute-unspecific HF membrane, created filtrate further processed in "tubular" section with nanotechnologically manufactured T-membrane allowing passage of solutes to be resorbed (http://content.karger.com/ProdukteDB/produkte.asp?Aktion=ShowAbstract&ProduktNr=223997&ArtikelNr=85882).

No sorbents are needed also in bio-artificial kidney of David Humes (25). Principle of his device is depicted in Fig. 10: Blood of the patient to be treated enters first a conventional haemofilter.

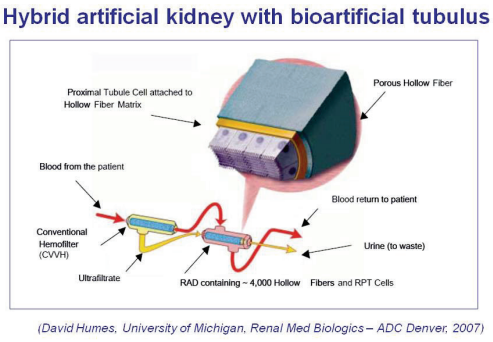
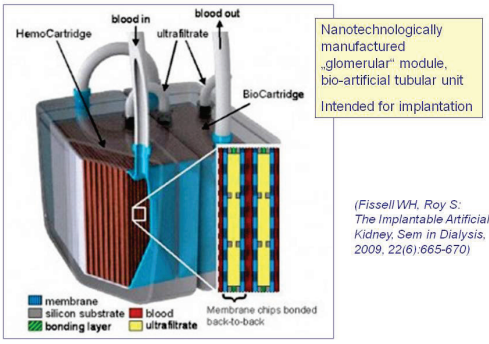


Fig. 10: WAK construction with bioartificial tubulus (D. Humes, 2007): Conventional haemofilter is used in the first (glomerular) stage, generated filtrate further processed in a special dialyzer with inner surface of the fibres coated with

monolayer of living epithelial tubular cells to do the same resorption as in tubules of biological kidney. Membrane in the bio-artificial tubulus protects cells of a donor from direct contact with blood of the patient treated with the device.

Filtrate from the first filter proceeds to the second capillary membrane device. Inner surface of its fibres are covered by a monolayer of living human tubular epithelial cells. Those cells do precisely the same what they normally do in tubules of a biological kidney – they resorb all for the body valuable substances from the primary filtrate to the blood which brought from the first filter to the outside fibres compartment of the second one. The device worked very well in the first clinical trials.



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Problems appeared when the cells started to grow and form thicker layer. However, Saito in Japan seems to have found a remedy recently – he started adding growth inhibition factor to the monolayer substrate (26) and the monolayer character of the cellular coating remained preserved. This success made him to consider construction of also the "glomerular" part of the device in a similar "bioartificial" way. To make the list of "bioartificial" construction complete, the device developed by Fissel and Roy must be mentioned (27). In principle, it is similar to Humes´s arrangement but from the very beginning it is being developed as an implantable device. Fig. 11 shows a picture of their device recently released on the Internet.

WAK pitfalls and realistic expectations

Reasons for the development of WAK do appear clear and reasonable: attenuation or complete removal of unphysiological variation in body chemistry seen in intermittent therapy (WAK has always been perceived as a synonymum to continuously running device), augmented in the last decade by an economic factor – expectations of lower treatment costs of RRT in chronic renal failure patients. Utilisation of convective principle (haemofiltration) is certainly better than diffusion-based process (haemodialysis) as the spectrum of solutes transported convectively across an artificial membrane is much closer to sieving spectrum of glomerular membrane and does not depend on molecular weight as is the case with diffusion. To mimic the second stage of nephron function – tubular resorption, most current WAK constructions rely on sorbents. Indeed, they can effectively eliminate huge amount of dialysis or substitution fluid needed in conventional therapies. However, an ideal sorbent which would have a mirror-like sorption spectrum compared to tubular function (what is not resorbed in tubules goes to "drain" as the final urine while what is not adsorbed on a sorbent remains in the body) has yet to be developed. Because of saturation with adsorbed waste metabolites, sorbent cartridges also need rather frequent exchanges. There are theoretically two technical alternatives to sorbent use – combination of electrodialysis, filtration and osmosis or membranes with selective permeability to waste metabolites only (to be manufactured by a nanotechnological process). Unfortunately, development of neither of those two possibilities is advanced enough to allow us to think about routine application in a near future.

To compare prospects and expectations of PD- and HD(HF)-based WAK constructions, there are three factors to consider. Easy control of fluid removal to continuously control patient hydration presents no problem in HD(HF)-based devices with direct access to blood, while it is much more difficult in PD-based devices. Precisely the opposite is safety of the access. Access to vascular system needed for an externally worn WAK is the major risk factor of those constructions. In fact, subjective fears of undetected disconnection of the extracorporeal circuit on the side of both physicians and patients themselves may entirely hamper introduction of an even perfect device into clinical use. Much better in this respect would be an implantable WAK permanently incorporated in patient´s vascular system once the issue of sorbent cartridge exchange is solved (e.g. by magnetically

assisted HD). The last issue to consider is degree of improvement in treatment physiology offered by a particular WAK construction. In this expectation, both systems are about equal. Continuous extracorporeal blood cleansing has been a standard treatment modality in acute renal failure for the last 25 to 30 years. Benefits of a truly continuously run PD-based device may be less apparent. But it is not just replacement of 10 to 12 litres of solution per day, as used in currently the most wide-spread PD modality – the CAPD (continuous ambulatory peritoneal dialysis) by only 2 litres and 2 to 3 sorbent cartridges. Circulation of the peritoneal solution via the cartridge keeps concentration of all catabolites in it permanently low which in turn keeps the difussional transport across the peritoneal membrane high all the time, not just at the beginning of each exchange as in conventional CAPD. It is very well seen on measurement of total excreted amount of urea on a physical model of PD shown in Fig. 12.

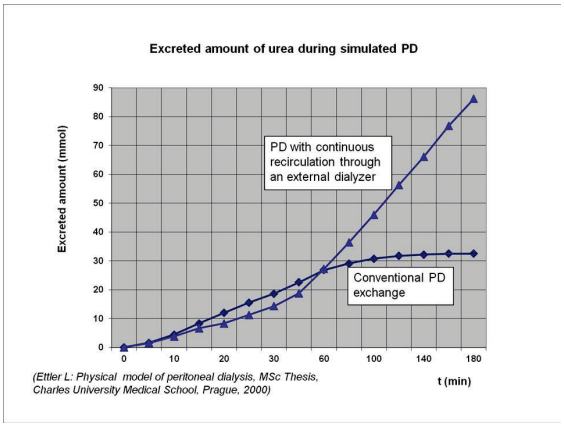

Fig. 12: Comparison of the total removed amount of urea during a simulated 3-hour PD: bottom curve – conventional PD exchange (rapid decrease in waste metabolites transport due to increasing concentration in dialysate during the exchange); upper curve – PD with the same amount of dialysate cleaned on-line by circulation through an external dialyzer keeping the transport high all the time (adapted from Ettler L: Physical model of peritoneal dialysis, MSc Thesis, Charles University Medical School, Prague, 2000).

In the TAC/TAD plot (Fig. 1), excretion of this magnitude would add to already low TAD value (achieved by conventional CAPD) also TAC values quite close to the "healthy region".

Those few bio-artificial or hybrid constructions developed so far have been surprisingly successful in *in vivo* trials unparalleled in purely technical WAK devices. Large scale application of those devices would however need to build up an entirely new infrastructure considering their rather short storage time and possible need of nutrient delivery during the idle storage time to keep the cell cultures alive.

Last but not least factor to consider in estimation of future needs and development directions of renal replacement therapy is development in the field of regenerative medicine, which, however, is well beyond the scope of this article.

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