# Animal Trials of Wearable Apparatus for Peritoneal Dialysis

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## Introduction

Chronic kidney failure (CKF) is a pathological condition which can be characterized by lowering metabolite and water removal rate and insufficient organism's homeostasis [1]. In 2010 the number of patients suffering from end-stage kidney failure (ESKF) excided two million people [2], [3]. Nowadays kidney transplantation is the only method of ESKF treatment. Alas, the amount of donor kidneys is not enough to supply all patients with donor organs. Organ rejection is another problem which can occur after kidney transplantation. In view of problems listed above renal replacement therapy (RRT) is vital necessity for patient with CKF. Blood purification and ultrafiltration are the main functions of RRT. There are two widespread RRT modalities commonly used nowadays: hemodialysis (HD) and peritoneal dialysis (PD). Although both methods provide sufficient blood purification, they have the following disadvantages: hemodialysis requires about 150 liters of dialysate per procedure, thus this therapy can be performed only in specialized dialysate centers. Moreover HD can cause low blood pressure and blood clots in dialysis access. Peritoneal dialysis requires frequent (4-6 per day) exchange of spent solution for peritoneal dialysis which increases the probability of peritoneal cavity contamination. Peritonitis is the main issue of PD which causes inflammation of peritoneal cavity and makes further PD procedures impossible.

Dialysate regeneration is method of spent solution purification which can potentially solve issues listed above. One of the major challenges of dialysate regeneration is urea elimination, since this metabolite is poorly removed by sorbent materials. Alternative dialysate regeneration methods such enzymatic and electrochemical methods can be use as alternative methods for urea removal; however chemical byproducts of electrolysis and urea hydrolysis are the main disadvantages of these methods. In this case different dialysate regeneration approaches can be combined to overcome these issues. For example combination of enzymatic and sorbent methods provides adequate urea and ammonia elimination and at the same time allows maintaining dialysate ion concentration in wearable artificial kidney (WAK) [4]. Therefore different variations of dialysate regeneration methods can be potentially used in WAK technology.

In this work combination of sorption and electrochemical methods was applied as dialysate regeneration approach. Sorption method can clean waste dialysate from different organic products of patient's metabolism including nitrogen bound substrate such as uric acid and creatinine and aromatic substrates such as phenol and p-cresol [5]. This method can also control ion concentration and pH of the dialysate. However most sorbents including ion exchange resins and majority of activated carbon modification have low capacity for urea, which is the main downside of sorption method. For purpose of urea elimination electrochemical method can be applied. This method can continuously eliminate urea from the solution by means of direct anode oxidation. Urea oxidation rate depends on different parameters such as current density, active anode surface, electrode type, solution ion composition, pH of the solution etc. Ability to regenerate working electrodes and urea elimination effectiveness are the main advantages of this method. However free-chloride and chloride-bound substrates generate during electrolysis. In addition electrochemical method acidifies solution during electrolysis and changes its ion composition. Intensive gas generation should also be taken into consideration. Therefore dialysate regeneration system based on this method requires additional degassing unit, post-treatment sorbent column and pH stabilizer for a proper and save functioning. Preliminary studies of this method were performed in the following papers: [6], [7].

In this study WAK with regeneration unit based on sorbent and electrochemical methods was tested on animals.

## Materials and Methods

In this work dialysate regeneration by means of sorbent and electrochemical methods was applied in animal trials. Animal trials were performed with usage of the following solutions for peritoneal dialysis: Fresenius Balance (glucose 1.5 %) and Extraneal (Baxter). Initial pH of both solutions was 5.4. Fresenius contains glucose as an osmotic agent (glucose concentration – 1.5%). Extraneal contains icodextrin as an osmotic agent. Composition of the solutions is presented in tables 1 and 2.

**Table 1:** Fresenius Balance (glucose 1.5 %)

| Ion | Concentration, mmol/l |
|---|---|
| Calcium ($Ca^{++}$) | 1,75 |
| Sodium ($Na^{+}$) | 134,0 |
| Magnesium ($Mg^{++}$) | 0,5 |
| Chloride ($Cl^{-}$) | 103,5 |

**Table 2:** Extraneal (icodextrin – 75 g/l)

| Ion | Concentration, mmol/l |
|---|---|
| Calcium ($Ca^{++}$) | 1,75 |
| Sodium ($Na^{+}$) | 133,0 |
| Magnesium ($Mg^{++}$) | 0,25 |
| Chloride ($Cl^{-}$) | 96 |

Peritoneal WAK system with described dialysate regeneration unit was tested on two dogs with weight 15 kg. Dialysate solution changed every 12 hours. Concentration of ions and nitrogen-bound substrates in dialysate was measured every hour. Scheme of the experiment is presented on figure 1.

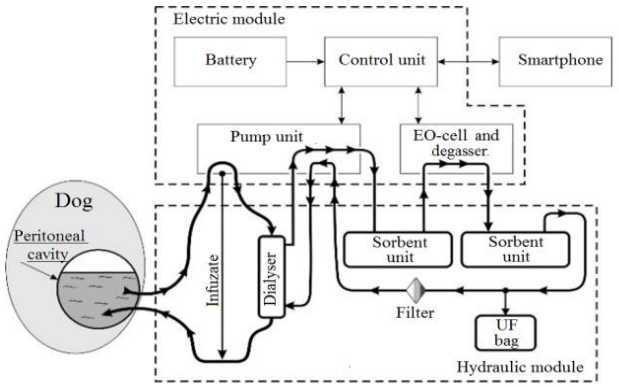


**Figure 1:** Experimental scheme of animal trials (UF – ultrafiltrate, EO-cell – electrochemical cell)

Experimental set-up included WAK system with dialysate regeneration module connected to dog's peritoneal cavity through catheter, control unit and receiving device (smartphone) for WAK-system control. Dialysate regeneration unit included dialyzer, sorbent units and electrolyzer. Dialyzer blocked protein and high-molecular substrates, thus preventing protein contamination of pumps and electrochemical cell. Sorbent units eliminated uric acid, creatinine and electrolysis byproducts, while electrochemical cell oxidized urea. Regenerated solution then came back to peritoneal cavity. The following materials were used in dialysate regeneration unit: sorbent units were filled with activated carbon FAS (100 g per unit); for urea elimination Ti/Pt electrodes with cumulative surface 300 $cm^2$ were added in EO-cell. Obtained results were compared with the following referent values [8]: urea 4–6 mmol/l, creatinine up to 176 μmol/l, uric acid up to 160 μmol/l.

Biotechnical system was divided on two parts. The first part was animal peritoneal cavity connected to dialyzer through the catheter (intracorporeal circuit). Fresh dialysate pumped into cavity. Wasted solution then came in the dialyzer where uremic metabolites diffused through the membrane to the dialysate in extracorporeal circuit. In extracorporeal circuit solution circulated through the dialysate regeneration unit. Dialysate circulation was performed by three peristaltic pumps: one in the intracorporeal circuit and two in the extracorporeal circuit.

Acute kidney disease (AKD) was provoked by infusion of mixture of 3 ml Diclophenac and 15 ml Ultravist. AKD was lately confirmed by blood test. To prevent catheter damage and animal injure the subject animal was sedated during the experiment.

Concentration of nitrogen-bound substrates, ion composition and pH were measured on biochemical analyzer Stat Fax 3300. Control of dialysate regeneration unit functioning was performed through the laptop. In particular electrochemical cell performance (such as current density and time of electrolysis) was controlled manually through laptop software.

## Results

The main results of medical trials are presented on figures 2 and 3

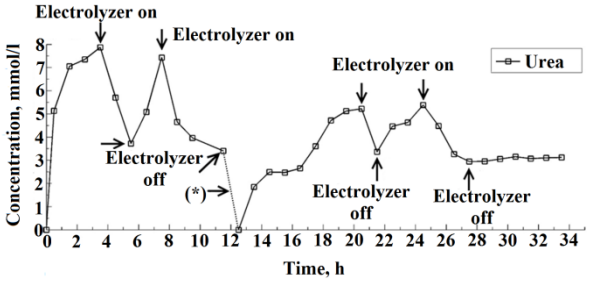


**Figure 2:** Urea concentration dynamics in the dialysate during WAK animal trials

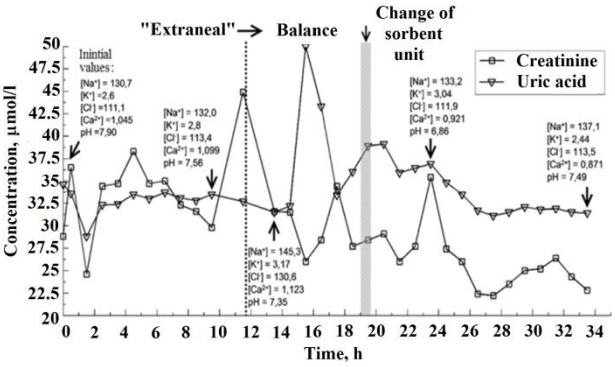


**Figure 3**: Creatinine and uric acid concentration dynamics in the dialysate during WAK animal trials

Developed dialysate regeneration unit effectively eliminated nitrogen-bound metabolites due to their adsorption on activated carbon and direct anodic oxidation. While creatinine and uric acid concentrations in dialysate solution did not exceed 50 μmol/l, urea concentration increase was observed during the experiment. To prevent intensive chloride byproduct generation EO cell worked only when urea concentration was close to 10 mmol/l. Overall nitrogen-bound substrates concentration stayed on physiological level during the trials and did not exceed critical values.

Necessity of electrolysis time control was the main issue of tested dialysate regeneration unit. In case of low urea concentration free-chloride and chloride-bound substrate generation becomes the main anode reaction. To eliminate these byproducts additional sorbent units are needed [9]. Moreover additional electrodes for urea detection have to be developed and applied to the system. Electrochemical cell functioning thus has to be automated. As a result electrochemical cell should work only if urea concentration in the solution gets close to or exceeds 10 mmol/l.

Another main obstacle of dialysate regeneration was poor potassium elimination. During animal trials potassium concentration increasing was observed. During the first hour of experiment potassium concentration in dialysate drastically increased from 0 to 2.6 mmol/l. After that potassium concentration steadily increased during peritoneal dialysis procedure. Twelve hours later potassium end concentration was 3.17 mmol/l. Next twelve hours after dialysate change potassium concentration continued increasing. In future version of dialysate regeneration unit specialized ion exchange resins will be needed for potassium elimination.

During dialysate regeneration chloride concentration increased which was also observed which can be explained by the following processes: ion diffusion through peritoneal membrane in the solution; ion generation during anode electro-oxidation process. The second phenomena can be explained by low urea concentration in the solution. As urea concentration drops below 6–8 mmol/l, generation of chloride gas, chloride-bound byproducts and chloride ion become the main anode process on anode surface. Thus electrochemical method can be effective in case of high urea concentrations (15 mmol/l and higher). Chloride-bound substrates generation can be decreased by EO-cell working mode control. For that development of specific urea sensor is essential.

## Discussion

Overall presented dialysate regeneration unit eliminated nitrogen-bound substrates from spent dialysate and maintained their concentration on physiological level. Activated carbon and sorbent materials in general are effective in case creatinine and uric acid elimination. In addition specific types of activated carbon maintain pH and ion concentration on appropriate level. However sorbent method was ineffective in case of urea elimination. For urea concentration control electrochemical method was applied. Despite of its efficiency this method had following restrictions: chloride gas and chloride-bound substrates are the main byproducts of electrolysis, thus additional dialysate treatment was required; electrochemical method is ineffective on urea concentrations below 5 mmol/l ergo additional urea sensor for EO-cell work is needed. The main disadvantage of presented system – lack of fine-dispersed sorbents for protein elimination, which have to be added in the next step of WAK development. System also requires additional ion-exchange resins for potassium and chloride elimination

## Conclusions

Presented dialysate regeneration unit for WAK-system effectively removed nitrogen-bound substrates. It did not affect dog's physiological state; however additional biocompatibility tests are required. For effective electrochemical cell functioning additional urea sensor might be needed. To remove proteins, protein-bound substrate and high-molecular substrates fine-dispersed sorbents are needed. Presented dialysate regeneration unit can be used in further WAK development.

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