A Simulation Study On Transcellular and Transcapillary Fluid Shifts Induced By Hemodialysis

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Abstract: *In this study, we developed a computer model to analyze body fluids volume variations, especially plasma volume changes. Also, serum sodium concentration and Blood Urea Nitrogen (BUN) changes were simulated using a combined model for transcapillary and transcellular fluid shift. Model predictions were found to be in good agreement with values which had been measured by Kimura et al[12,13]. Urea and sodium transfer across the dialyzer membrane and transcellular fluid shifts which occurs in response to the sodium and the other electrolytes transfer, were modeled. Tanscapillary fluid and proteins exchange occurs too, which influences hydrostatic and oncotic pressures in interstitial and capillary space due to ultrafiltration (UFR). With regard to that any of transcapillary and transcellular models itself cannot discuss fluids and electrolytes behavior in body, introducing lymphatic system, interstitial and capillary protein content as nonlinear behavior and transcellular electrolytes exchange, we simulated a new model. Using this model, it is possible to predict serum sodium concentration, blood osmolality, Blood Urea Nitrogen (BUN) after dialysis and plasma volume during dialysis in order to better hemodialysis therapy. Also, it is possible using model optimization and feedback blood volume controlling and monitoring systems to avoid hypotension. Using rational dialysate concentration with respect to serum sodium concentration changes can be used to reduce disequilibrium syndrome.*

Key Words: *transcapillary, transcellular*, Hemodialysis, Ultrafiltration, Electrolytes Exchange, Protein Exchange

Introduction

A person with renal failure has little or no kidney function. The signs and symptoms of renal failure, a state called uremia, are extremely diverse and frequently appear to point to disease of other organs. Failure to regulate the excretion of salt and water places the body at risk of fluid overload. Fluid may accumulate in the subcutaneous tissues as edema or in serous cavities as excess peritoneal fluid or pleural effusion. Peripheral edema is unsightly but harmless, whereas pulmonary edema can compromise gas exchange in the lungs, leading to shortness of breath, hypoxia and ultimately death[4].

Hemodialysis is a process whereby water and metabolic waste products are removed from the blood by an artificial kidney. During hemodialysis, blood circulates from an artery into a dialyzer and returns through a vein. Inside the dialyzer blood is separated from dialysate fluid by a semi-permeable membrane. Movement of solutes from the blood to the dialysate occurs by diffusion across the membrane. Concentration of solutes in the blood can be controlled by the composition of the dialysate. Excess body fluid is ultrafiltrated from the blood side of membrane due to negative pressure. A patient with renal failure uses an artificial kidney for several hours a day for a few days out of each week.

The incidence of intradialytic disequilibrium syndrome and symptomatic

hypotension has increased significantly among dialysis patients over the last ten years[2,12,13]. Also, It has been demonstrated that the use of dialysate with a high Na^+ concentration reduces these complications[12,13].

The model for transcapillary fluid exchange has been established for a long time[1,12]. It's impossible, however, to directly apply this model to hemodialysis therapy, because transcellular fluid exchange is also essential to simulate the change in plasma volume during hemodialysis.

In this work, the combination of these two models has been introduced to enable simulation of the change in plasma volume, serum sodium concentration and **BUN** during hemodialysis.

Model Assumptions

1. Body water is distributed in three uniformly mixed compartments approximating the intracellular(ICF), interstitial(ISF), and plasma(PL) volumes. The sum of the ISF and PL compartments forms the extracellular (ECF) compartment. The total body fluid (TBF) is the sum of the ICF and ECF volumes.
2. Water movement between the ICF and ECF compartments is analogous to movement across the cell membrane and is caused only by change in the concentration of osmotically active solutes in the ICF and ECF compartments [2,4,13].
3. The amount of osmotically active solutes in the ICF compartment doesn't change during dialysis. Water movement to or from the compartment causes changes in the concentration of osmotically active solutes in the ICF compartment[2,4,13].
4. Sodium diffuses freely across the capillary wall. Since sodium is contained mostly in the ECF compartment this assumption allows description of sodium kinetics during dialysis by a one-compartment model.
5. At the beginning of dialysis there is osmotic equilibrium. This allows calculation of the pre-dialysis concentration of osmotically active solutes from the pre-dialysis plasma sodium concentration.
6. Water movement between the ISF and PV is similar to movement across the capillary wall, which is proportional to the forces of capillary pressure, plasma oncotic pressure, interstitial hydrostatic pressure, and interstitial osmotic pressure[1,2,4,12].
7. Interstitial compliance is nonlinear[1].
8. Protein leaks across the capillary wall during dialysis with a certain content [16]. On the other hand, moves from ISF to capillary space with reabsorbsion with a certain content[16]. Proteins also moves from ISF to capillary compartment using lymph flow with a constant content[], so that lymph flow variations versus ISF pressure is nonlinear[1,16].
9. Osmotic pressure in PV and ISF compartments is nonlinear functions of their protein content[1,12].
10. PV and ISF protein content have nonlinear differential relations with their protein mass and compartments volume[16].
11. Protein mass variations in PV and ISF compartments are balanced with capillary filtration, reabsorbsion and lymph flow[1,12,14].

Figure1 is a schematic of combined model. As you see, filtration, reabsorbsion and lymph flow make fluid and protein to

move between ISF and PV. Water and electrolytes move between ECF and ICF through cell membrane by several mechanisms. As blood flows through dialyzer water and materials exchange occurs between plasma and concentrate.

The Mathematical Model

In order to establish the model, intracellular and extracellular volume changes were simulated using mathematical formulation during hemodialysis.
By combining this model with transcapillary model plasma volume was also obtained.

Landis-pappenheimer equations have been used as basic relations for establishing transcapillary models[12,14];

$$F_A(t)=L_A\times[H_A-H_T(t)-\Pi_{PL}(t)+\Pi_T(t)] \quad \underline{1}$$

$$R_V(t)=L_V\times[\Pi_{PL}(t)-\Pi_T(t)-H_V+H_T(t)] \quad \underline{2}$$

in which filtration F_A and reabsorbsion R_V are expressed as functions of hydrostatic arterial A, venous V, interstitial T pressures and oncotic plasma Π_{PL} and interstitial Π_T pressures and also hydrolic permeability coefficients L of vessels. The oncotic pressures are expressed as functions of plasma and interstitial spaces protein contents as below;

$$\Pi_{PL}(t)=2.1\times C_{PL}(t)+0.16\times C_{PL}^{2}(t)+0.009\times C_{PL}^{3}(t) \quad \underline{3}$$

$$\Pi_T(t)=2.8\times C_T(t)+0.18\times C_T^{2}(t)+0.012\times C_T^{3}(t) \quad \underline{4}$$

transcellular and transcapillary models are combined by the equation;

$$ISF(t)=ECF(t)-PV(t) \quad \underline{5}$$

in which ISF, ECF and PV are interstitial, extracellular and plasma volumes respectively. Plasma volume is also obtained by;

$$\frac{dPV(t)}{dt}=-[F_A(t)+UFR]+R_V(t)+Q_{rl}(t) \quad \underline{6}$$

in which UFR is ultrafiltration rate and Q_{rl} is lymph flow rate which are obtained using reference [1] relations.

Plasma and interstitial protein contents are expressed as nonlinear functions of protein mass in these spaces and their volumes instead of kimura linear functions as reference[16].

The following equations were also used for transcellular part of the model as had been introduced in reference[2];

$$\frac{d}{dt}[TBF(t)]=-UFR(t) \quad \underline{7}$$

$$TBF(t)=ICF(t)+ECF(t) \quad \underline{8}$$

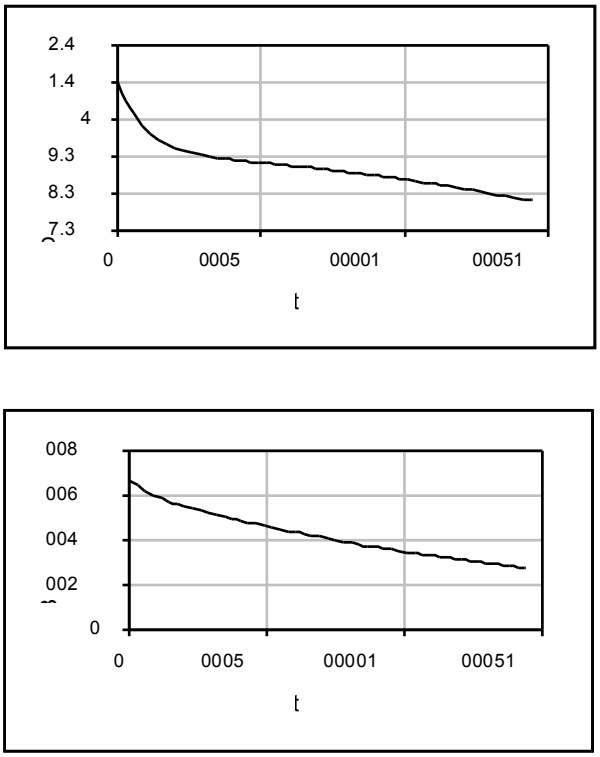
$$ECF(t)=\frac{TBF(t)}{[1+\frac{M_{U,i}(t)+M''_{eq,i}(t)}{M_{Na,e}(t)+M_{U,e}(t)+M_{eq,e}(t)}]} \quad \underline{9}$$

so that TBF, ICF, $M_{U,i}$, $M_{U,e}$, $M_{Na,e}$ are total body fluid volume, intracellular fluid volume, amount of urea in the intracellular pool, amount of urea in extracellular pool, amount of sodium in ECF and $M''_{eq,i}$, $M_{eq,e}$ are amount of different solutes in ICF and ECF as has been described in reference [2].

Equations solution

The combined model for transcapillary and transcellular simulation contains a set of coupled linear and nonlinear differential equations. This set was processed using "simulink" toolbox of MATLAB software. In each test, initial conditions and constant values of certain group of patients were

used. In order to validate model outputs, experimental values of Kimura et al[12,13] were used. In their work, the values of parameters were had been measured in five patients who had been studied on hemodialysis at three different dialysate sodium concentration equal to 7% below and 7% above the predialysis serum sodium concentration.



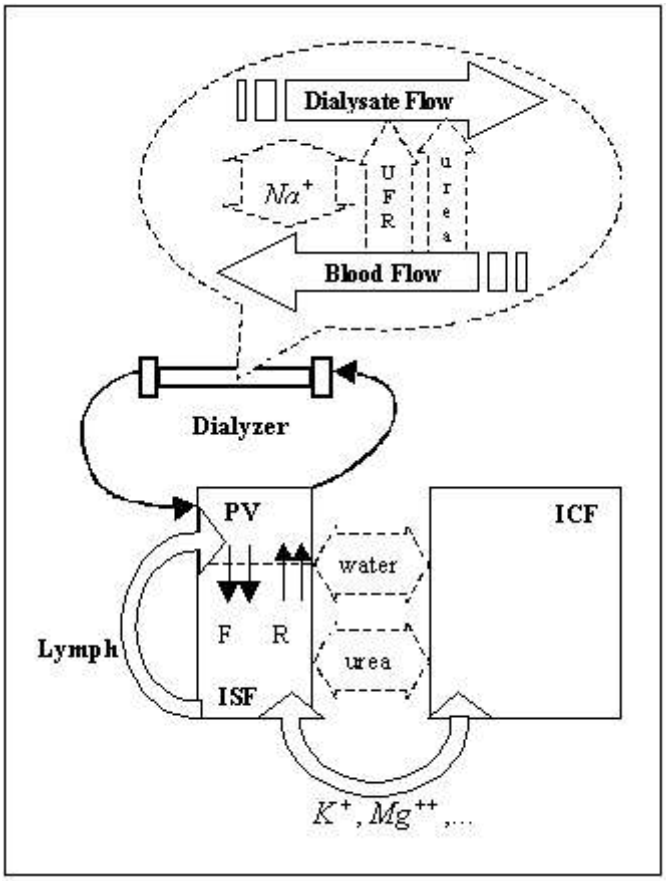


Fig1:Schematic diagram of combined simulated model.

Results

Figures 2 to 4 show plasma volume, serum sodium concentration and **BUN** changes during dialysis for the group of patients who were treated using high Na^+ concentrate as typical outputs.

Figures 2 and 3 show the trend, which is consistent with what the others obtained [1,3,4,5,8,12]. As we used average values of kimura et al, these trends are in excellent agreement with their results. Also, as you see in figure 4 the results of introduced model are in better agreement with measured data in comparison to kimura model.

In kimura model, there has been a significant difference in the value at 1 hr after the beginning of the high Na^+ hemodialysis. The present model can see the severe changes during first hour and cover them.

Fig3:BUN changes during dialysis with high sodium dialysate.

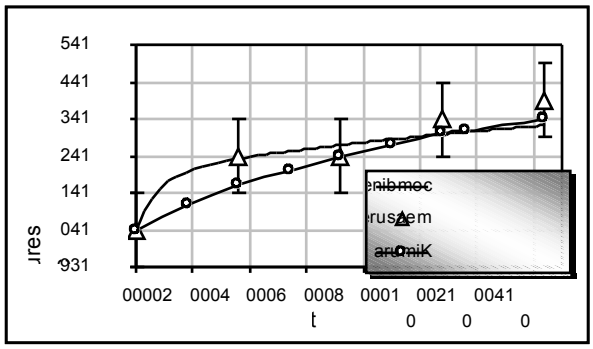


Fig4:A comparison between kimura model, combined model and measured values for serum sodium concentration.

Discussion and Conclusion

Several transcapillary and transcellular models have been proposed during past years. It is impossible; however, to directly apply these models to hemodialysis therapy, because transcapillary and transcellular fluid and materials exchanges occur together so that they are instantaneously engaged to each other. Also, some simplifications have been done in these models. Therefore, converting them into practical software and hardware in hemodialysis machines is a difficult problem.

The main goal of this study was to develop a combined biological model, which converge most of these models and experiences into one model using last researches in this field.

Based on literature survey, in recent researches[1] lymphatic system and interstitial compliance have been introduced as nonlinear behavior. Besides, fluid, sodium, and urea exchange across cell membrane and dialyzer membrane, also other electrolytes exchange across cell membrane had been considered as simplified behavior. But plasma and interstitial protein content changes, which had been considered before as linear behavior[4,12], has been introduced as nonlinear behavior, using Schneditz et al idea[8].

As you see, the model in some circumstances like serum sodium concentration changes in dialysis with high Na^+ concentrate had results better than Kimura model. In fact, severe extracellular osmolarity changes was hidden in the Kimura model point of view. On the other hand, in dialysis with normal and low concentrate, Kimura model introduced better results.

There have been some error resources for this simulation. Not to consider the other electrolytes exchange especially potassium except to sodium across dialyzer membrane is the most important one.

The present model can be optimized and examined by different experimental values and used to obtain the best UFR and dialysate profiles for individual convenient dialysis.

The use of the mathematical model allows us to obtain an approximate estimation of the amount of sodium (and probably the other electrolytes) which are actually removed during hemodialysis. The correct choice of the UFR and dialysate concentration profiles, able to remove a given amount of sodium per session is a difficult problem, the solution of which depends on several different simultaneous factors: mainly, the initial concentration of sodium and other solutes in the blood and in the extracellular pool, the UFR, dialysis operative conditions, and the duration of session. All these factors interact in complex nonlinear ways during treatment, thus making qualitative predictions of sodium and fluid extraction unreliable.

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