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Sodium Modeling During Controlled Hypertonic CVVHD for ICP Management Using a Multiscale Mathematical Model

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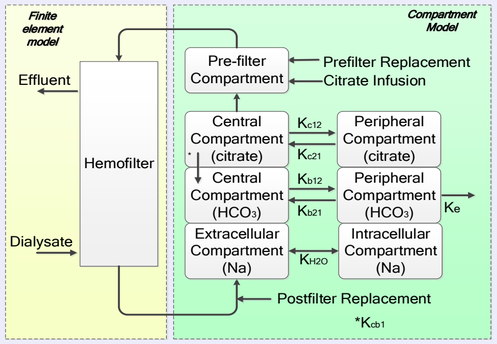
Introduction

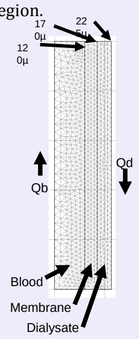
Manipulation of extracellular electrolytes is an important part of the management of critically ill patients. Controlled hypernatremia can play a role in the management of intracranial hypertension. The ability to predict CRRT operating parameters and/or results of therapy may prove useful in the application of this therapy. Extracellular sodium during CRRT is determined by a number of interrelated factors that make prediction of sodium levels non-trivial, and include sodium concentrations and infusion rates of Na citrate anticoagulation, replacement fluid, dialysate, intravenous fluids and urine. In addition, volume of sodium distribution, water balance between intracellular and extracellular compartments, and convective and diffusive clearance by the hemofilter play additional important roles. The extracorporeal exchange of sodium is complex, depending on the interactions of blood flow, ultrafiltration rate, dialysate rate, intraluminal and membrane diffusion, protein concentration polarization, and others. A multiscale mathematical model, which incorporates model features based on vastly different physical scales, previously developed for citrate balance (CRRT 2012) was extended to include sodium compartment transport, preserving the principles of hemofilter hollow fiber transport (microliter scale) while including the dynamics of sodium, citrate and bicarbonate distribution and metabolism in the body (liter scale).

Model Overview



The finite element geometry was implemented as a 2D axisymmetric representation of the cross section of a hollow fiber and its associated interior blood region and exterior dialysate region.

The hemofilter dimensions and membrane characteristics were based on the M60 hemofilter with the AN69S membrane (dimensions shown at right).



The mesh consisted of 275,000 elements with thin boundary layer elements used on the fluid boundaries of the membrane. The MUMPS (Multifrontal Massively Parallel Solver) was used to obtained solutions.

The model was developed in and solved with COMSOL Multiphsics® finite element modeling software (http://www.comsol.com)

Finite Element Hollow Fiber Model

The hollow fiber model was adapted from a finite element model previously presented (CRRT 2012) by extending it to include sodium in addition to citrate and bicarbonate, and is briefly described here. The hollow fiber unit was modeled as a 2-dimensional axisymmetric geometry corresponding to the dimensions of the M100 hollow fiber length.

Momentum balances

The blood phase and dialysate phase momentum balances are described by the incompressible Navier-Stokes equations, where u is the velocity vector, p is pressure, ρ is density, and η is dynamic viscosity:

$$\rho\frac{\partial u}{\partial t}-\nabla\cdot\eta(\nabla u+(\nabla u)^T)+\rho(u\cdot\nabla)u+\nabla p=0,\qquad \nabla\cdot u=0$$

The membrane momentum balance is described by the Brinkman equations for porous flow, where κ is the permeability coefficient, and F is osmotic pressure:

$$\rho\frac{\partial u}{\partial t}-\nabla\cdot\eta(\nabla u+(\nabla u)^T)-(\frac{\eta}{\kappa}u+\nabla p-F)=0,\qquad \nabla\cdot u=0$$

Mass balances

Mass balances were established for the diffusible solute in each of the blood, membrane and dialysate phases using the convection-diffusion equation:

$$\frac{\partial c_s}{\partial t}+\nabla\cdot(-D_s c_s+c_s u)=0$$

Diffusion coefficients for solutes were calculated from equations in Fournier (1999). A separate mass balance was established for protein in the blood phase. Plasma osmotic pressure is calculated from the Landis-Pappenheimer equation, local hematocrit is calculated from changes in plasma volume, and local plasma and blood viscosity are calculated from the approach by Merrill.

Boundary conditions

Boundary conditions for blood and dialysate inlet and outlet were set to represent experimental conditions of blood flow, dialysate flow, and circuit pressures. At the blood-membrane boundary, flux and pressure were conserved, protein flux was zero, and the concentration gradient for solutes was determined by the sieving coefficient, where σ is the Staverman reflection coefficient:

$$\frac{C_m}{C_b}=\Theta,\qquad \Theta=1-\sigma\frac{e^{Pe_m}-1}{e^{Pe_m}-\sigma},\qquad Pe_m=\frac{J_v(1-\sigma)}{P_m}$$

Compartment Model

Sodium and citrate/bicarbonate dynamics were each represented by two compartment (ECF/ICF and central/peripheral) models, respectively, with distribution, metabolism and elimination using ordinary differential equations. The model is based on established sodium models (Mann 2000) and citrate and bicarbonate dynamics (Kornberg 1952])and Kramer (2003).

$$V_{central}\frac{dC_{citrate[central]}}{dt}=C_{citrate_{in}}\dot{Q}_{citrate_{in}}-V_{central}C_{citrate_{central}}K_{c12}+V_{periph}C_{citrate_{periph}}K_{c21}-V_{central}C_{citrate_{central}}K_{cb1}$$

$$V_{periph}\frac{dC_{citrate[periph]}}{dt}=V_{central}C_{citrate_{central}}K_{c12}-V_{periph}C_{citrate_{periph}}K_{c21}+V_{periph}C_{citrate_{periph}}K_{cb2}$$

$$V_{central}\frac{dC_{hco3[central]}}{dt}=-V_{central}(C_{HCO3_{central}}-C_{HCO3_{init}})K_{b12}+V_{periph}(C_{HCO3_{periph}}-C_{HCO3_{init}})K_{b21}$$

$$V_{periph}\frac{dC_{hco3[periph]}}{dt}=V_{central}C_{citrate_{central}}K_{cb1}\cdot 3+V_{central}(C_{HCO3_{central}}-C_{HCO3_{init}})K_{b12}$$
$$-V_{periph}(C_{HCO3_{periph}}-C_{HCO3_{init}})K_{b21}-V_{periph}(C_{HCO3_{periph}}-C_{HCO3_{init}})K_e$$

$$V_{ECF}\frac{dC_{Na}}{dt}=\dot{Q}_{citrate}C_{Na_{citrate}}+\dot{Q}_{replace}C_{Na_{replace}}+\dot{Q}_{dialysate}C_{Na_{dialysate}}-\dot{Q}_{effluent}C_{Na_{effluent}}-\dot{Q}_{urine}C_{Na_{urine}}$$

$$\frac{dV_{ECF}}{dt}=\dot{Q}_{citrate}+\dot{Q}_{replace}+\dot{Q}_{dialysate}-\dot{Q}_{effluent}+K_{H2O}(C_{Na\_ECF}-C_{ICF})$$

$$\frac{dV_{ICF}}{dt}=-K_{H2O}(C_{Na\_ECF}-C_{ICF})$$

Results

Compartment parameter estimation

The compartment parameters for central and peripheral volumes of citrate and bicarbonate distribution (Vc and Vd) and rate constants (Kc12, Kc21, Kb12, Kb21, Kcb1 and Ke) were determined by least squares fit to experimental data of citrate pharmacokinetics from Kramer et al (2003) using the SNOPT (Sparse Nonlinear OPTimizer) optimization solver in COMSOL:

$$Vc=0.075L/kg \qquad Vp=0.280L/kg$$
$$K_{c12}=1.79\times10^{-3} \qquad K_{c21}=6.06\times10^{-4}$$
$$K_{b12}=6.00\times10^{-5} \qquad K_{b21}=9.96\times10^{-4}$$
$$K_{cb1}=1.77\times10^{-3} \qquad K_e=1.70\times10^{-2}$$

The initial extracellular and intracellular compartment volumes for sodium kinetics (V_{ECF} and V_{ICF}) were based on body weight, and varied with sodium-induced water shifts. The hydraulic mass transfer coefficient for water (K_{H2O}) was obtained from Mann (2000).

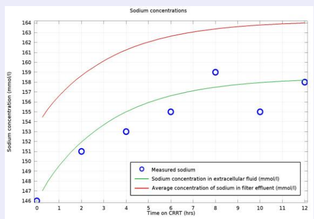
Clinical cases

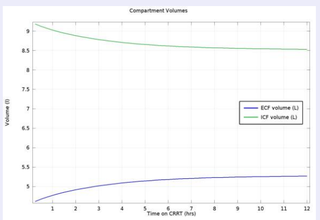
Two cases of CRRT used for maintenance and control of hypernatremia during treatment for traumatic brain injury with intracranial hypertension are presented below. Data are presented at baseline and for 12 hours following initiation of therapy.

Case 1

3 year old traumatic brain injury, 23 kg.

Qblood	80 mL/min	4% Na citrate	130 mL/hr
Qreplacement	750 pre/500 post mL/hr	Cna replacement	158.7 mmol/l
Qdialysate	500 mL/hr	Cna dialysate	158.7 mmol/l

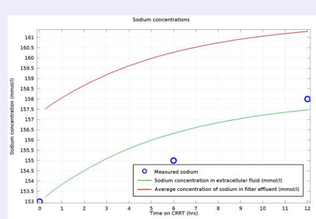


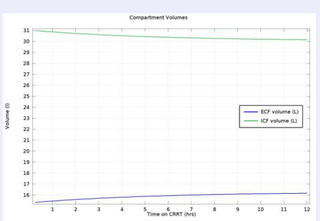


Case 2

19 year old traumatic brain injury, 77.2 kg.

Qblood	150 mL/min	4% Na citrate	150 mL/hr
Qreplacement	1000 pre/1000 post mL/hr	Cna replacement	158.7 mmol/l
Qdialysate	1000 mL/hr	Cna dialysate	158.7 mmol/l





Discussion

- This model allows the study of various operating parameters on the dynamics of sodium, citrate and bicarbonate during continuous therapies such as SCUF, hemofiltration, hemodialysis and hemodiafiltration. These parameters include all modifiable treatment parameters, such as blood flow rate, flow rates of replacement fluid and dialysate, pre- vs. postfilter infusion, ultrafiltration rate, and filter characteristics. They also include patient parameters such as body size, presence of edema, and citrate metabolic rate.
- Sodium prediction by the model during hypertonic CRRT is reasonably close to clinically measured valued in two cases.
- The model is calibrated with citrate and bicarbonate kinetic data collected over several hours, and therefore would be less reliable when used for lengthy simulations, such as several days. The model is also limited by the use of a two compartment representation of citrate and bicarbonate dynamics, which are likely to be more complex.
- Likewise, the use for long-term prediction of sodium kinetics would also be limited, since not all sources of sodium loss are identified, such as iv fluids, enteral feeds, and variation in urine output and sodium concentration.
- Future directions include the addition of chloride and calcium kinetics to identify the development of citrate lock

Summary

- The use of mathematical modeling can provide useful insight into the operating characteristics of processes such as hemofiltration and hemodialysis.
- Multiscale models such as the one presented herein can combine the intricacies of transport at the small scales present within the hollow fibers of a hemofilter with large scale transport representing distribution at the organism level.
- The model permits the simulation of various treatment parameters to evaluate the potential impact of different treatment strategies.

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