Simulation Study on the Efficacy of Toxin Removal by Pulsatile Flow in Blood Purification Systems that use Semipermeable Membranes

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Key Words : Blood purification system, Semipermeable, Numerical model, Hemofiltration, High flux dialysis, Hemodiafiltration, Pulsatile pump

Abstract

Using numerical models, we investigated the efficiency of toxin removal using pulsatile flow in blood purification systems that use semipermeable membranes. The model consisted of a three-compartmental mass transfer model for the inside body and a solute kinetics model for the dialyzer. The model predicted the toxin concentration inside the body during blood purification therapy, and the toxin removal efficiencies at different flow configurations were compared quantitatively. According to the simulation results, the clearances of urea and β_2 microglobulin (B2M) using a pulsatile pump were improved by up to 30.9% for hemofiltration, with a 2.0% higher urea clearance and 4.6% higher B2M clearance for high flux dialysis, and a 3.9% higher urea clearance and 8.2% higher B2M clearance for hemodiafiltration. These results suggest that using a pulsatile blood pump in blood purification systems with a semipermeable membrane improves the efficacy of toxin removal, especially for large molecules and hemofiltration treatment.

1. Introduction

Various studies have examined methods of using a pulsatile mechanism to increase the UF rate without increasing the flow rate. Runge *et al.* [1] demonstrated enhanced molecular clearance and UF rate using a pulsatile pump in an *in vitro* experimental study. Previously, we quantified the contribution of pulsatile flow to the UF rate, and discovered the reasons for the enhanced transmembrane pressure (TMP) and UF rate using a pulsatile pump through *in vitro* experiment using bovine whole blood [2]. However, both studies are limited to *in vitro* test, and they did not demonstrate toxin clearances, toxin removal ratio, and temporal variation of toxin concentration inside body in various blood purification systems such as hemofiltration, hemodiafiltration, and high flux dialysis.

To predict solute kinetics inside body according to different flow types, mathematical simulation is useful. There are several mathematical models of dialysis systems [3-6]. To explain the transport of fluids and solutes through cell membranes and vessel walls during hemodialysis, Ursino *et al.* [4] developed a mathematical model consisting of three compartments: intracellular fluid, interstitial fluid, and plasma. They assumed that dialyzer toxin clearance is a constant parameter in the model. Depner *et al.* [7] created a mathematical model for the solute kinetics in the dialyzer and quantified the effects of blood and dialysate flow on dialyzer toxin clearance. Nevertheless, no mathematical model can explain the effect of flow type on toxin concentration inside the body. Therefore, we integrated a numerical model that includes a three-compartmental mass transfer model of Ursino *et al.* [4] and a solute kinetics model for the dialyzer of Depner *et al.* [7]. Using this model, we investigated the toxin clearance, toxin removal ratio, and temporal variation of the toxin concentration inside the body when the different type of blood pump was applied, once with a pulsatile pump and once with a standard roller pump.

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2. Material and Method

2.1. Description of model

The mass transfer inside the body that occurs during blood purification therapy can be explained roughly using body solutes and fluid exchange kinetics, as described by Ursino *et al.* [4]. To simulate the effect of flow configuration in a dialyzer on UF rate, we combined Depner *et al.*'s model of mass transfer inside a dialyzer [7]. The body-fluid components can be classified into intracellular fluid, interstitial fluid, and plasma components. The body-solute components can be classified into intracellular and extracellular components. Figure 1 is a schematic diagram of the combined mass transfer model used in this study.

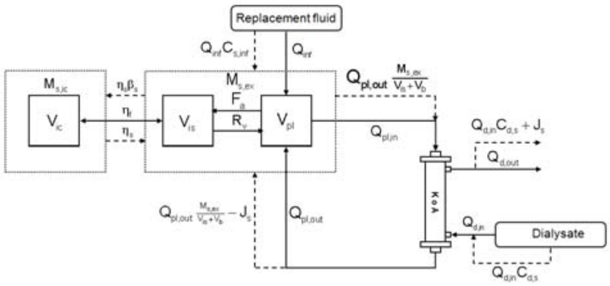


Fig. 1. The compartmental model used to describe body fluid exchange and solute kinetics.

2.2. Numerical method

For the mass and volume transfer model, the governing equations consist of 12 coupled first-order differential equations. The forward Euler method using a 1-s time step was used to integrate the system of differential equations numerically. The calculation time was 4 h for the blood purification treatment and an observation time of 1 h.

2.3. Parameters and initial conditions

The mean blood flow rates were set to 300 mL/min. Parameters such as TMPm, K_{uf}, mean inlet and outlet pressures in the blood circuit, and mean inlet and outlet pressures in the dialysate circuit were adopted from the previous paper [2]. T-PLS (BHK Inc., Korea) and AK 95 (Gambro Inc., Germany) were used to represent pulsatile pump and standard roller pump respectively. Fig. 2 shows the pressure waveform at the dialyzer inlet in the blood circuit produced by the T-PLS pulsatile pump and the AK95 roller pump. The mean pressures are 180 mmHg in both cases.

Hemofiltration treatment: K_{uf} was taken from the calculated data at a mean blood flow rate of 300 mL/min in the previous paper. As there is no dialysate flow in hemofiltration system, the dialyzer inlet and outlet pressures in the dialysate circuit are zero.

Hemodiafiltration treatment: K_{uf} was taken from the data calculated under a mean blood flow rate of 300 mL/min in our previous paper [2]. The dialysate flow rate was set to 300 mL/min as same as the blood flow rate.

High flux dialysis treatment: The mean dialyzer inlet and outlet pressures in the dialysate circuit were assumed to have the same values as in the blood circuit and are applied to the model to maximize the convective toxin removal. K_{uf} was taken from the calculated data under a mean blood flow rate of 300 mL/min in our previous paper [2].

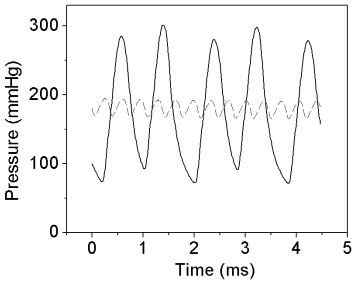


Fig. 2. Pressure waveform at the dialyzer inlet in the blood circuit produced by the T-PLS pulsatile pump and the AK95 roller pump using bovine whole blood.

3. Result

3.1. Validation of the models

To validate the mass transfer model, the urea concentrations in the intracellular and extracellular compartments during 4 h of treatment and 1 h of observation were calculated and compared with the *in vivo* data. As shown in Fig. 3, the plasma urea concentration profile was very similar to the experimental results.

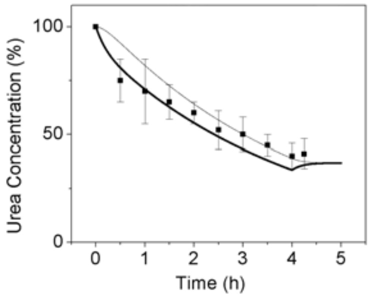
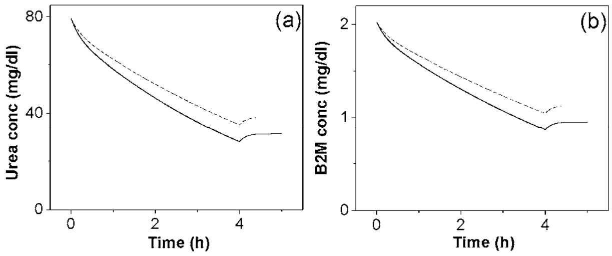


Fig. 3. Percent change in the intracellular urea concentration (thin line) and plasma urea concentration (thick line) in the simulation and *in vivo* experiment (rectangles).

3.2. Toxin removal efficiency

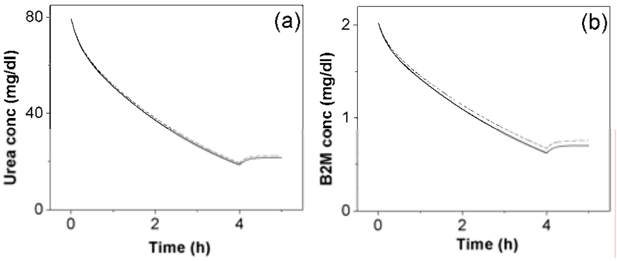
Hemofiltration: When T-PLS pulsatile pump was applied to the model, the convective clearances of urea (molecular weight, 60 Da; sieving coefficient, 1) and B2M (molecular weight, 11,800 Da, sieving coefficient, 0.8) were calculated to 182 and 145 mL/min, respectively. When AK95 roller pump was applied, the convective clearances of urea and B2M were 139 and 111 mL/min, respectively (Table 1, Fig. 3)



(a) (b)

Fig. 4. Simulated changes in the plasma urea (a) and B2M (b) concentrations with the T-PLS (solid line) and AK95 (dashed line) pumps during hemofiltration treatment.

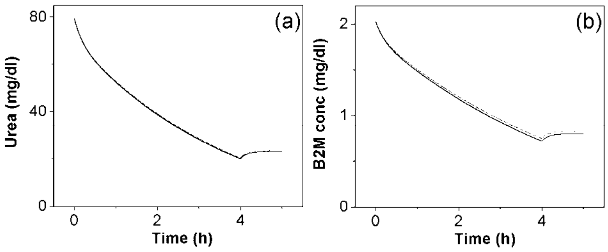
Hemodiafiltration: The diffusive clearances of urea and B2M were 232 and 151 mL/min, respectively, with blood and dialysate flow rates of 300 mL/min. When T-PLS pump was applied to the model, the added convective clearances of urea and B2M were 34 and 59 mL/min, respectively, and the total clearance rates of urea and B2M were 266 and 210 mL/min, respectively. When AK95 pump was applied, the added convective clearances of urea and B2M were 24 and 43 mL/min, respectively, and the total clearance rates of urea and B2M were 256 and 194 mL/min (Table 1, Fig. 4).



(a) (b)

Fig. 5. Simulated changes in the plasma urea (a) and B2M (b) concentrations with the T-PLS (solid line) and AK95 (dashed line) pumps during hemodiafiltration treatment.

High flux dialysis: The diffusive clearance rates of urea and B2M were 232 and 151 mL/min, respectively, with blood and dialysate flow rates of 300 mL/min. Internal UF and BF were calculated to be 79 mL/min for the T-PLS pump and 59 mL/min for the AK95 pump using Eq. (18). Therefore, the added convective clearance rates of urea and B2M for the T-PLS pump were 9 and 29 mL/min from Eq. (15), and calculated the total clearances of urea and B2M were 250 and 182 mL/min, respectively. The added convective clearances of urea and B2M for the AK95 pump were 13 and 23 mL/min, and the total clearance rates were 24 and 174 mL/min, respectively (Table 1, Fig. 6).



(a) (b)

Fig. 6. Simulated changes in the plasma urea (a) and B2M (b) concentrations with the T-PLS (solid line) and AK95 (dashed line) pumps during high flux hemodialysis treatment.

Table 1. *Clearances and toxin reduction ratios of urea and B2M*

	Hemofiltration		Hemodiafiltration		High flux dialysis	
	TPLS	AK95	TPLS	AK95	TPLS	AK95
K_{ur}	182	139	266	256	250	245
K_{b2}	145	111	210	194	182	174
URR	65%	56%	77%	76%	75%	74%
BRR	57%	48%	69%	67%	65%	63%

URR, urea reduction ratio; BRR, B2M reduction ratio.

4. Discussion

By developing an integrative model combining a three-compartmental mass transfer model for inside body and a solute kinetics model for the dialyzer in the blood purification system, we predicted the toxin concentration variation inside the body during blood purification treatment and compared toxin clearances and reduction ratios when pulsatile and roller pumps were used. Our previous *in vitro* study demonstrated the superiority of the pulsatile pump with regard to the TMP and UF rate [2]. The results of our previous study indicated higher TMPm variation under the same blood flow rate and higher K_{uf} variation under the same TMPm conditions with pulsatile pump than roller pump. With these data, the toxin clearances, toxin reduction ratio, and temporal variation of the toxin concentrations inside body during treatment between the pulsatile and roller pump groups were evaluated using the mathematical model.

The model was validated by comparing the temporal variation of the simulated plasma urea concentrations during hemodialysis with *in vivo* experimental data. In blood purification therapy, small molecules such as urea are easily removed by diffusion and convection, while large molecules such as B2M are removed primarily by convection [7]. This is explained by the observation that the sieving coefficient (index of convective clearance) of B2M is 80% that of urea and the overall mass transfer coefficient (index of diffusive clearance) of B2M is only 30 % that of urea.

When the T-PLS pulsatile pump was applied for hemofiltration therapy, 30.9 % higher clearances of urea and B2M clearance were simulated (Table 1). Hemofiltration treatment uses convection only, which improves by using the pulsatile pump. The diffusive clearance of urea and B2M are all zero in hemofiltration treatment. The convective clearances depend on the UF rate and sieving coefficient of the dialyzer. Consequently, the increased UF rate using a pulsatile pump proportionally enhances the convective clearance of urea and B2M.

When the T-PLS pulsatile blood pump was applied for hemodiafiltration treatment, the urea clearance increased by only 3.9%, while the B2M clearance increased by 8.2% (Table 1). This was probably because hemodiafiltration uses diffusion and convection mechanisms simultaneously for toxin removal, while the pulsatile blood pump enhances convection only in the model, which affects convective clearance; data supporting this concept were reported in our previous paper [2]. The diffusive clearance of a small molecule, such as urea, is so high with hemodiafiltration treatment that the convective clearance of urea decreased relatively according to Eq. (15). The diffusive clearance of the B2M was very low compared to that of urea (30 % of urea clearance), and so the added convective clearance of B2M was relatively high. Therefore, the augmentation of urea removal was much less than that of B2M using the pulsatile blood pump.

When the T-PLS pulsatile pump was applied for high flux dialysis, the urea clearance increased by only 2.0%, while the B2M clearance increased by 4.6% (Table 1). As high flux dialysis treatment uses diffusion and convection simultaneously for toxin removal (as in hemodiafiltration treatment), the increase in B2M removal efficiency was much higher than that in urea removal efficiency using the pulsatile blood pump.

Using a pulsatile blood pump for a blood purification system that uses a semipermeable membrane increases the convective toxin clearance by enhancing UF, especially for large molecular toxins such as B2M. This increased toxin clearance could result in reduced treatment times and associated costs. Several animal studies have shown that a pulsatile blood pump in a blood purification system can maintain a physiologically stable hemodynamic state and can be used as an alternative to roller pumps [8, 9]. In the present study, we investigated the toxin clearance and reduction ratio and compared the toxin concentration inside the body when the different flow configurations were applied. Although this study was a simulation, our results may be used as reference data when considering the use of pulsatile pumps in clinical blood purification systems to increase the efficiency of the UF rate, toxin clearance, and toxin removal ratio.

5. Conclusion

This paper presented a numerical simulation model for estimating the toxin clearance, toxin removal ratio, and toxin concentration inside the body in response to blood purification therapies such as hemofiltration, hemodiafiltration, and high flux dialysis. The numerical results matched the *in vivo* results, allowing the analysis of quantitative toxin removal in the body associated with two different types of blood pump. In comparison with the AK95 roller pump, the T-PLS pulsatile pump increased the clearance of small molecular toxins, such as urea, and large molecular toxins, such as B2M, at identical mean flow rates. We concluded that a pulsatile blood pump is more efficient to remove blood toxins as well as excessive water in blood purification systems that use semipermeable membranes.

Acknowledgement

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References

(1) Runge, T.M., et al., 1993, "Hemodialysis: evidence of enhanced molecular clearance and ultrafiltration volume by using pulsatile flow." Int J Artif Organs, vol. 16, pp. 645-52.

(2) Lim, K., et al., 2008, "Quantitative Analysis of Pulsatile Flow Contribution to Ultrafiltration." Artif Organs,. Accepted 18 Apr.

(3) Ziolko, M., J.A. Pietrzyk, and J. Grabska-Chrzastowska, 2000, "Accuracy of hemodialysis modeling." Kidney Int, vol. 57, pp. 1152-63.

(4) Ursino, M., et al., 2000, "Prediction of solute kinetics, acid-base status, and blood volume changes during profiled hemodialysis." Ann Biomed Eng, vol. 28, pp. 204-16.

(5) Kimura, G., J.C. Van Stone, and J.H. Bauer, 1984, "Model prediction of plasma volume change induced by hemodialysis." J Lab Clin Med, vol. 104 pp. 932-8.

(6) Akcahuseyin, E., et al., 2000, "Simulation study of the intercompartmental fluid shifts during hemodialysis." ASAIO J, vol. 46, pp. 81-94.

(7) Depner, T. and L. Garred, 2004, "Solute transport mechanisms in dialysis", in Replacement of Renal Function by Dialysis., W. Horl, et al., Editors., Kluwer Academic Publishers: Norwell. pp. 73-93.

(8) Ruperez, M., et al., 2003, "Continuous venovenous renal replacement therapy using a pulsatile blood pump." Pediatr Nephrol, vol. 18, pp. 29-32.

(9) Ruperez, M., et al., 2005, "Comparison of a tubular pulsatile pump and a volumetric pump for continuous venovenous renal replacement therapy in a pediatric animal model." Asaio J, vol. 51, pp. 372-5.