A MATHEMATICAL MODEL FOR THE ULTRAFILTRATION THROUGH MAMMALIAN ARTERY WALL

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Introduction

Ultrafiltration is driven by a gradient of chemical potential which can be described in terms of the hydrostatic and osmotic pressure across the wall. Because the endothelium can be considered as a major barrier to transporting plasma proteins, filtration across the artery wall would be expected to give rise to a concentration polarization boundary layer at the interface between blood and wall, with the concentration of protein increasing from bulk value towards the interface (Colton *et al.*, 1972, Keller, 1974). Under these circumstances, the filtration rate would be affected by increasing osmotic pressure which is caused by increasing the concentration of polarized layer at the artery wall's interface. The degree of concentration polarization (expressed as the interfacial concentration relative to the bulk value) depends on the bulk concentration and transmural pressure (Blatt *et al.*, 1970). To examine these factors, several authors have proposed various experimental approaches in which the concentration of protein was altered in perfused vessels (Mason *et al.*, 1977; Huxley and Curry, 1985), or the transmural pressure (Dull *et al.*, 1991) was varied. In such an event concentration polarization effect has been shown to be insignificant. However, Fry (1986) indicated that in the de-endothelium vessel pressurized with a non-stirred solution, each protein's concentration at the intimal (a inner layer of artery wall which is under the endothelium cell) interface was found to be greater than its concentration in the serum's bulk phase. Various mathematical models have been developed for interpreting these previous experimental results; however, most of them failed to give quantitative descriptions.

In this work, the author propose a simple mathematical model based on a concentration polarization (CP) effect, which may be significant, particularly for the vessels filled with non-stirred fluid, in the case of high bulk protein concentration and high transmural pressure. The model can successfully interpret a set of experimental data, reported by Lever

and Sharifi (1987), of the measured water flux through isolated rabbit common carotid artery, in the absence of luminal flow, in response to both varying pressures and changing perfusate albumin concentrations. Applying this mathematical model provides a means for explicitly estimating the mass transfer coefficient, the Peclet number, and the degree of concentration polarization at the artery wall's interface. It is worthy to point out that the first theoretical model including the CP effect was presented by Tarbell *et al.* (1988); however, the influence of varying transmural pressure has not been clearly demonstrated in their study. Moreover, their model does not allow an explicit calculation of these transport parameters rather just give a approximate estimation by the curve fitting method. In addition, the current model, compared with these previous models, provides more information about these transport parameters.

1. Theoretical Model

The filtration rate J_V through the wall of an artery, as through any other membrane, may be represented by the equation of Kedem-Katchalsky (1958):

$$J_V = L_p[\Delta P - \sigma_d \Delta \pi] \quad (1)$$

where ΔP and $\Delta \pi$ are the transmural hydrostatic pressure (THP) and osmotic pressure differences, respectively, and σ_d is the reflection coefficient. In this model hydraulic conductivity L_p is pressure-independent and L_p can be linearly extrapolated from the experimental data reported by Lever and Sharifi (1987). Based on their data ($L_p = 2.584 \times 10^{-8} \text{ cm sec}^{-1}(\text{mmHg})^{-1}$ at $C_b = 2 \text{ g/dl}$ and $L_p = 1.987 \times 10^{-8}$ at $C_b = 7 \text{ g/dl}$), L_p at $C_b = 0 \text{ g/dl}$ can be consequently calculated as $2.823 \times 10^{-8} \text{ cm sec}^{-1}(\text{mmHg})^{-1}$. In the event of concentration polarization, the protein concentration increases toward the wall from the bulk value C_b to a value C_w at the interface of the artery wall and the osmotic pressure difference across the artery wall will then be $\pi(C_w)$. Thus, Eq. (1) can be rearranged as

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$$\pi(C_w) = \frac{1}{\sigma_d} \left[\Delta P - \frac{J_V}{L_p} \right] \quad (2)$$

By using the measured J_V (Lever and Sharifi, 1987) and assuming σ_d as 1.0 for albumin in an artery with an intact endothelium (Renkin and Curry, 1982), then the osmotic pressure can be calculated by Eq. (2). The measured osmotic pressure, π , of the varying albumin concentration has been well correlated by Tarball *et al.* (1988) as

$$\pi(C_w) = 2.43 C_w + 0.1 C_w^2 + 0.0061 C_w^3 \quad (3)$$

where $\pi(C_w)$ is in mmHg and wall albumin concentration C_w is in grams per deciliter. Once the $\pi(C_w)$ was calculated from Eq. (2), the C_w could be easily estimated from Eq. (3).

Revealed from the images which is obtained by using stereological electro-micrographic methods (Carey-Smith *et al.*, 1975; Perry 1980), the structure of endothelium's intercellular clefts appears to be a channel of approximately 1 μm in length and 20 nm in width. These experimental observations also showed that in the inter-endothelial cleft, there exist tight junction (two adjacent endothelium's membranes appearing fused or touching) regions of roughly 0.1 μm in length and 5 nm in width. The transmural water pathway is assumed to be predominant through the endothelium's intercellular clefts and the media's interstitial space (Renkin and Curry, 1982; Weinbaum *et al.*, 1983). Consequently, an idealized configuration for describing the concentration polarization layer formed in the endothelium cleft may be depicted as Fig. 1. Based on this configuration, the restricted solute flux J_s in small channels can be derived as the following equation (Anderson and Quinn, 1974; Yan *et al.*, 1986).

$$J_s = -\xi D_\infty \frac{dC}{dz} + \chi C J_V \frac{A}{A_p} \quad (5)$$

In Eq. (5) D_∞ is the free solution Brownian motion diffusivity, dC/dz is the cross-section-averaged concentration gradient along the channel. ξ is the observed ration of pore-to-bulk solute diffusivity (based on bulk concentration differences) and χ is the sieving coefficient (ration of solute to solvent velocity in the channel). They both reflect the additional drag on the solute by the channel's wall effect. The A/A_p may be defined as the ratio of total wall surface area A to the channel cross area A_p which is associated with the water pathway (the outer region of the intercellular cleft). Then the fluid velocity in the channel can be expressed as $J_V A/A_p$. If there is no solute flux through the channel and D_∞ , ξ and χ are assumed to be

Fig. 1 The configuration of concentration polarization effect for modelling the mechanism of protein transport through endothelium cleft

constant, Eq. (5) can be integrated from the bulk phase $z=0$, where $C=C_b$, through the thickness of the concentration polarization layer $z=\delta$, where $C=C_w$, to give

$$C_w = C_b e^{P_e} \quad (6)$$

where P_e is the Peclet number defined as

$$P_e = \frac{\chi \delta}{\xi D_\infty} \cdot \frac{A}{A_p} \cdot J_V \quad (7)$$

Unlike the previous study of Tarbell *et al.* (1988) in which the value of δ was prescribed in their model, in the current model this parameter can be explicitly determined and compared with the results of physiological observations (the details shown in the Section Results and Discussion). Since C_w have been already determined by Eq. (3), the values of Peclet number can be subsequently calculated from Eq. (6). The mass transfer coefficient, defined as $\xi D_\infty/\delta$, and then Eq.(7) can be rearranged as

$$k = \frac{\xi D_\infty}{\delta} = \frac{\chi}{P_e} \cdot \frac{A}{A_p} \cdot J_V \quad (8)$$

The estimated values for ξ and χ for the arbitrary shape solutes in a slit-shaped pore are limited. However, for spherical solutes an analytical equation has been obtained using the centerline approximation (Curry, 1974)

Fig. 2 Peclet number of the concentration polarization layer at artery wall versus transmural hydrostatic pressure (THP) for solutions containing 2 or 7 (g/dl) bovine serum albumin (BSA)

$$\xi \cong \Phi [1 - 1.004\lambda + 0.418\lambda^3 + 0.21\lambda^4 - 0.169\lambda^5 + O(\lambda^6)] \quad (9)$$

$$\chi \cong \frac{\Phi}{2} (3 - \Phi^2) \left[1 - \frac{\lambda^2}{3} + O(\lambda^3) \right] \quad (10)$$

where $\lambda = R_s/h$ is the ratio of spherical solute's radius R_s to the slit half-width h ; the component $O(\lambda^6)$ and $O(\lambda^3)$ represent the truncation error as a magnitude of λ^6 and λ^3 , respectively. Φ is partition coefficient which can be given as:

$$\Phi = 1 - \lambda \quad (11)$$

To calculate ξ and χ , the endothelium cleft can be approximately modeled as 20 nm width channel and albumin molecule may also be considered as a sphere (radius is about 3.5 nm). Under such an approximation, the value of λ is calculated as 0.35, and then ξ and χ may be calculated, from Eqs. (9), (10) and (11), as 0.43 and 0.80, respectively. The estimated value for the A_p/A was unavailable. However, some inspections of transmission micro-graphs suggested that it may be roughly 0.001. Equation (8) allows the value of k to be estimated by using the calculated P_e and the measured J_v which was reported by Lever and Sharifi (1987).

2. Results and Discussion

The Peclet number, the mass transfer coefficient, and the degree of concentration polarization at interface of artery wall have been estimated using the

Fig. 3 Mass transfer coefficient of the concentration polarization layer at artery wall versus transmural hydrostatic pressure (THP) for solutions containing 2 or 7 (g/dl) bovine serum albumin (BSA). The data for the solution of 2 (g/dl) at $\Delta P = 70$ mmHg coincide with the data for the solution of 7 (g/dl)

Fig. 4 Polarization ratio of the concentration polarization layer at artery wall versus transmural hydrostatic pressure (THP) for solutions containing 2 or 7 (g/dl) bovine serum albumin (BSA)

theoretical analysis, combined with the set of previous experimental data. **Figures 2, 3 and 4** summarize these results. Both Peclet number and the degree of polarization layer increase with an increasing transmural pressure in a non-linear manner; however, both decrease with an increasing albumin concentration. There is a marked effect of transmural pressure on

Peclet number and the degree of concentration polarization between 70 and 180 mmHg. No significant difference in the mass transfer coefficient occurs with an increasing pressure when pressure exceeds 100 mmHg.

Figure 2 shows the calculated value of Peclet number for these various THP and bulk concentration. Those values are comparable with those in other studies (Truskey *et al.* 1981, Tarbell *et al.* 1988). Like many filtration systems, in the present system, the Peclet number quasi-linearly increases with THP at low pressure region and increases to a lesser extent with THP at a high pressure range. As THP is increased, more solute is brought to the artery wall surface and C_w presumably increases, thereby increasing the back-transport rate of solute into the main stream. Eventually, because of a balance of forward-convective transport of solute and back-diffusive transport, no significant increase occurs in the Peclet number for a further increasing pressure. Blatt *et al.* (1970) indicated that for the solution with a high bulk concentrations, the low pressure would be expected for the C_w reaching to the gel concentration of the macrosolute C_g . Once C_w approaches to C_g , the flux could be expected to be pressure-independent. This could account for why the pressure-independent region occurred at a lower pressure for the case of the higher bulk concentration solution. Furthermore, in the current system the curve of filtration rate against pressure and the Peclet number-pressure curve at $C_b=7$ g/dl are obviously slightly smaller than those at $C_b=2$ g/dl. Peclet number obtained in the current system also indicates that diffusive transport is dominating at $C_b=7$ g/dl while convective transport is prevailing at $C_b=2$ g/dl when pressure exceeds 70 mmHg.

The filtration of proteins leads to a formation of the concentration polarization layer on membrane surface behaving as part of the membrane. The concentration of this layer depends on size, shape and degree of hydration of the solute (Cheryan, 1986), but depends to a lesser extent on membrane properties beyond a certain pressure (Openg and Zydney, 1991). Cheryan (1986) summarized a number of experimental data from five different filtration systems to show that the mass transfer coefficients k of BSA for these systems generally range from 0.9 to 26×10^{-6} m/s. The mass transfer coefficients obtained in the current study range from 8.08 to 18.24×10^{-6} m/s (see Fig. 3) which is comparable with these values of Cheryan (1986). However, this estimated value of k for the current systems still needs further confirmations due to the lack of corresponding data published previously. Figure 3 also indicates that mass transfer coefficients are less dependent on pressure when THP exceeds 70 mmHg. In this study mass transfer coefficient at $C_b=2$ g/dl is slightly higher than those at

$C_b=7$ g/dl, except for THP at 70 mmHg. Since the system with a large value mass transfer coefficient is usually associated with an extremely high pressure drop across membrane, this may account for the reason why the lower bulk concentration solution ($C_b=2$ g/dl) has a higher k owing to its lower osmotic pressure.

By using the calculated observed ratio of pore-to-bulk solute diffusivity ξ (about 0.43) and assuming the free diffusion coefficient of albumin to be 1.6×10^{-7} cm²/s (that found for diffusion in 1.5% hyaluronic acid (Winlove and Parker, 1984), then the polarized layer's thickness δ , as calculated from Eq. (8), ranges from 0.37 to 0.85 μ m, which is roughly the length of the outer region of the intercellular cleft. This result implied that the concentration polarization layer is formed from the region of tight junction to the lumen/endothelium interface and this is consistent with the earlier assumption reflected in Fig. 1.

Figure 4 shows that the predicted polarization ratio C_w/C_b at $C_b=2$ g/dl is higher than C_w/C_b at $C_b=7$ g/dl. Thus, in the current system, the maximum concentration at the artery wall's surface is predicted to be 19.1 g/dl. Kozinski and Lightfoot (1972) did not observe gel formation in aqueous bovine serum albumin solutions until the protein concentration exceeded 40 g/dl. This could be the reason why the fully pressure-independent region in filtration rate did not occur in the Lever and Sharifi's system (1987).

Conclusion

An application of the current simple mathematical model, combined with the previous experimental data, facilitates the quantitative estimation of a number of transport parameters through rabbit's artery wall. The influences of bulk concentration and transmural pressure on the filtration rate are well modelled by invoking the concentration polarization effect. The current model also provides a reasonable interpretation for an idealized configuration which is modelled based on the characteristic dimensions of the structure of endothelium cleft revealed from the experimental investigations of rabbit's artery.

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Nomenclature

A	= total surface area of isolated artery wall
A_p	= channel cross area
C_b	= bulk concentration

C_w	= concentration at tight junction of endothelium cleft	
D_∞	= diffusivity in glycocalyx	[cm ² /sec]
h	= slit half-width of endothelium cleft	
J_V	= filtration rate	[cm/sec]
J_s	= solute flux	[moles/sec]
L_p	= hydraulic conductivity	[cm sec ⁻² (mmHg) ⁻¹]
P_e	= Peclet number	
R_s	= radius of solute	
Z	= depth counted from the interface of CP layer	
χ	= sieving coefficient	
ξ	= observed ration of pore-to-bulk solute diffusivity	
δ	= thickness of concentration boundary layer	
ϕ	= partition coefficient	
λ	= ratio of albumin's diameter to endothelium cleft's width	
σ_d	= reflection coefficient of albumin at endothelium tighter junction	
ζ	= restriction coefficient	
ΔP	= transmural hydrostatic pressure difference	
$\Delta \pi$	= osmotic pressure difference	[mmHg]

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