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Physiological Interpretation of Solute Transport Parameters for Peritoneal Dialysis

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A mathematical model for solute distribution within the tissue due to combined processes of diffusion and convective transport through the tissue, through the capillary wall, and by lymphatic absorption, during the exchange of the solute between an organ and external medium is applied for the description of the transport of small, middle and macro – molecules. The analytical solutions of the transport equations for the steady state are described. A parameter that characterizes the concentration profiles, the penetration depth, for combined diffusive and convective transport through the tissue is described as a function of the penetration depths for pure diffusive and pure convective transport components. The equation for the solute transport across the tissue surface is similar to a phenomenological formula widely used for the description of clinical and experimental peritoneal dwell studies. The phenomenological transport parameters may therefore be interpreted using the local transport coefficients for the tissue, the capillary wall, and lymphatic absorption. Theoretical estimations of those parameters are in good agreement with clinical data about solute transport in patients on continuous ambulatory peritoneal dialysis.

Keywords: diffusion, convective transport, mathematical model, capillary wall, lymphatic absorption, perfusion

1. INTRODUCTION

Peritoneal dialysis is a medical treatment of patients with end stage renal disease aimed at removal of waste metabolites and uremic toxins as well as excess of water from patient's organism and regulation of the physiological status of body fluids (Gokal and Nolph, 1994). It consists in infusion of dialysis fluid into the peritoneal cavity where it dwells for a few hours. During peritoneal dialysis solutes, such as osmotic agents, buffer solutes, additives and drugs, are transported from dialysis fluid to the tissue, and inside the tissue are absorbed to blood and lymph. On the other hand, solutes, which are to be removed with peritoneal dialysate, are transported first from blood to the tissue and there they are partly absorbed with lymph and partly transported to dialysis fluid. The contribution of blood and lymph flows to the solute gradient, created within the tissue due to the presence of dialysis fluid at the tissue surface, results in characteristic

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solute concentration profiles within the tissue (Flessner et al, 1985b, 1997; Waniewski et al, 1999). For the description of this phenomenon the so called distributed model was formulated; however, it was applied in general only with numerical solutions, and analytical closed solution was applied mainly for diffusion (Patlak and Fenstermacher, 1975; Dedrick et al, 1982; Flessner et al, 1984; Leypoldt and Henderson, 1992; Waniewski et al, 1999), although an approximated solution was found also for combined diffusive and convective solute transport (Patlak and Fenstermacher, 1975).

In the present study, a theoretical analysis of combined diffusive and convective transport of solutes according to the distributed model is presented. The capillary wall is described as a heteroporous barrier for solute transport between blood and tissue (Rippe and Haraldsson, 1994). Lymphatic absorption of interstitial fluid and solutes is also included into the model. Therefore, all main factors that affect solute transport are taken into account and the model may be applied for the description of solutes with different size and transport characteristics in a unified approach (Flessner, 1991).

2. SOLUTE EXCHANGE BETWEEN BLOOD AND TISSUE

In the normal physiological conditions fluid circulates from blood to interstitium, from interstitium to lymphatic vessels, and with lymph back to blood. The hydrostatic and the oncotic pressures in blood and interstitial fluid regulate the exchange of fluid between blood and tissue. The fluid leaving blood is absorbed in the same amount from tissue as lymph. Whereas the lymphatic absorption is a bulk flow (i.e. with no sieving of absorbed solutes), macromolecules are sieved by the capillary wall. This process yields the concentration of solutes in the tissue, C_T, to be generally lower than in blood, C_B. The sieving effect is substantial for albumin and larger proteins. A theoretical description of the transport of macromolecules through the capillary wall is provided by the two pore model (Rippe and Haraldsson, 1994). The pore model is based on a concept of a cylindrical uniform pore across the membrane. Solute and fluid transport through the pore is evaluated using the hydrodynamic theory of fluid flow and theoretical description of diffusion and convective drag of spherical particles along the cylindrical pore (Deen, 1987). The theory provides so called restriction factors for diffusive and convective solute transport, which describe how much the solute transport is retarded due to the presence of the pore wall comparing to the free transport in an unbound medium (Deen, 1987; Rippe and Haraldsson, 1994).

The parameters used for the description of the transport through a pore are pore radius, r_P, pore length, Δ_Z, Stokes radius of the solute, r_S (calculated from the solute molecular weight), and fluid viscosity, η. The restriction factor for diffusion is presented as the ratio of the effective surface area of the pore cross-section, a_{eff}, over its nominal surface area, $a_0 = \pi r_P^2$ (Rippe and Haraldsson, 1994):

$$\frac{a_{eff}}{a_0} = \frac{(1-\alpha)^{9/2}}{1 - 0.3956\alpha + 1.0616\alpha^2}, \qquad (1)$$

where $\alpha = r_S/r_P$. Thus, the pore diffusive permeability is given by the following formula (Rippe and Haraldsson, 1994):

$$P = \frac{a_0}{\Delta z}\frac{a_{eff}}{a_0} D_W, \qquad (2)$$

where D_W is the diffusion coefficient for the solute in water, and a_{eff}/a_0 is given by equation (1). The retardation factor for convective solute transport is called in thermodynamics the sieving coefficient, S (with $S = 1 - \sigma$, σ being the Staverman reflection coefficient), and may be calculated as (Rippe and Haraldsson, 1994):

$$S = \frac{(1-\alpha)^2(2-(1-\alpha)^2)(1-\alpha/3)}{1 - \alpha/3 + 2\alpha^2/3}. \qquad (3)$$

The pore hydraulic conductivity, l_P, of the pore is described according to the Poisseuille law (Rippe and Haraldsson, 1994):

$$l_P = \frac{a_0}{\Delta z}\frac{r_S^2}{8\eta}. \qquad (4)$$

Multiplying P and l_P by the number of pores per unit membrane surface area one gets the global transport coefficients for the membrane.

According to the two pore model, the capillary is heteroporous with two sizes of equivalent pores: large pores (L) of radius about 200 – 300 Å, and small pores (SM) of radius about 40 – 50 Å (Rippe and Haraldsson, 1994). Diffusive permeability, $P_C a_C$ (where P_C is the diffusive permeability per unit capillary surface area, and a_C is the capillary surface area per unit tissue volume), hydraulic conductivity, $L_{PC} a_C$ (where L_{PC} is the hydraulic permeability per unit capillary surface area), sieving coefficient, S, and reflection coefficient, $\sigma = 1 - S$, for small and large pores may be calculated by adjusting formulas (2) – (4) to the available data about capillary transport (Rippe and Haraldsson, 1994). Large pores play the important role in the transport of macromolecules (of the size of albumin and larger) mainly by convective flow. Small pores are the main routes for the exchange of small and middle molecules. The number of large pores is much lower than the number of small pores.

The fluid flow through the capillary membrane (expressed per unit volume of the tissue) is the sum of the flows through the small and large pores, and each of these flows is regulated by the hydrostatic and oncotic pressure gradients through the capillary wall:

$$q_{VCP} = l_P a_P(\Delta P - \sigma_P \Delta\Pi), \qquad (5)$$

where index P denotes small (SP) or large (LP) pore. The solute flow, q_{SC} (per unit tissue volume), through the capillary wall may be described as:

$$\begin{aligned} q_{SC} = {} & k_{BT}(C_B - C_T) + S_{SP} q_{VSP} \\ & (F_{SP} C_B + (1 - F_{SP}) C_T) \\ & + S_{LP} q_{VLP} \\ & (F_{LP} C_B + (1 - F_{LP}) C_T), \end{aligned} \qquad (6)$$

where the diffusive mass transport coefficient k_{BT} is the sum of total diffusive permeability for small and large pores calculated as described above, and the coefficients F_P for small (SP) and large (LP) pores are given by the following formula:

$$F_P = \frac{1}{Pe_P} - \frac{1}{\exp(Pe_P) - 1}, \qquad (7)$$

where $Pe_P = S_P q_{VP} / k_{BTP}$ is the Peclet number for the pore (Rippe and Haraldsson, 1994).

Equation (6) may be presented as $q_{SC} = k_B C_B - k_T C_T$, where:

$$k_B = k_{BT} + S_{SP} q_{VSP} F_{SP} + S_{LP} q_{VLP} F_{LP}, \qquad (8)$$

$$\begin{aligned} k_T = {} & k_{BT} + S_{SP} q_{VSP}(1 - F_{SP}) \\ & + S_{LP} q_{VLP}(1 - F_{LP}). \end{aligned} \qquad (9)$$

Parameters k_B and k_T represent unidirectional clearances (per unit tissue volume) for transport from blood to tissue and from tissue to blood, respectively.

3. DIFFUSIVE AND CONVECTIVE TRANSPORT IN PERITONEAL DIALYSIS

In the case of driving forces that induce solute transport across the tissue (e.g. solute concentration gradient, which induces diffusion, and fluid flow, which induces convective transport) two transport parameters for the tissue have to be taken into account. These are: tissue diffusivity, D_T, and tissue sieving coefficient, S_T. Furthermore, the fluid flux across the tissue, j_{VT}, must be known. In the following, it will be assumed that j_{VT} is constant in time and does not depend on the position within the tissue.

The local solute balance within the tissue is described by the continuity equation:

$$\frac{\partial(\theta C_T)}{\partial t} = -\frac{\partial j_{ST}}{\partial x} + q_{SBTL}, \qquad (10)$$

where θ is void fraction, i.e. the fraction of tissue volume effectively available to the solute (assumed constant),

$$j_{ST}(x) = -D_T \frac{dC_T}{dx}(x) + S_T j_{VT} C_T(x) \qquad (11)$$

is the solute flux across the tissue, and

$$\begin{aligned} q_{SBTL}(x) &= k_B C_B - k_T C_T(x) + q_{VL} C_T(x) \\ &= -(k_T + q_{VL})(C_T(x) - \kappa C_B) \end{aligned} \qquad (12)$$

is the solute flow in the exchange between blood, tissue and lymph, where k_B and k_T are given by equations (8) and (9), respectively, and:

$$\kappa = \frac{k_B}{k_T + q_{VL}}. \qquad (13)$$

Parameter κ has an important physiological interpretation. In the state of equilibrium the fluid flow from blood to tissue is the sum of flows through the small and large pores, $q_{VC} = q_{VSP} + q_{VLP}$, and must be equal to the lymph flow from the tissue to blood, q_{VL}. Similarly, the flow of solute from blood to tissue, q_{SC}, must be equal to the flow of the solute absorbed from tissue by lymph, $q_{SL} = q_{VL}C_T$, i.e. $q_{SC} = q_{VL}C_T$. Using these two balance rules and equation (6) for q_{SC}, one gets that at the state of physiological equilibrium $C_{Teq} = \kappa C_B$, i.e. κ describes the ratio of the equilibrium concentration of the solute in the tissue over its concentration in blood.

In the steady state the description of the transport of solutes between blood and dialysate in the peritoneal cavity according to the distributed model is:

$$\frac{d}{dx}\left(-D_T\frac{dC_T}{dx} + S_T j_{VT} C_T\right) = -(k_T + q_{VL})(C_T - \kappa C_B). \tag{14}$$

Using non-dimensional variables $\xi = x/L$, where L is the width of the tissue layer, and a normalized concentration profile, Γ, defined as:

$$\Gamma(\xi) = \frac{C_T(\xi) - \kappa C_B}{C_D - \kappa C_B}, \tag{15}$$

where C_D is the solute concentration in dialysate, one may derive from equation (14) the following description of the steady state concentration profiles:

$$\frac{d^2\Gamma}{d\xi^2} - Pe_T\frac{d\Gamma}{d\xi} - \Phi^2\Gamma = 0, \tag{16}$$

where $Pe_T = S_T j_{VT}/P_T$ is the Peclet number for diffusive – convective transport across the tissue, $P_T = D_T/L$ is the diffusive permeability of the tissue layer, and $\Phi = L/\sqrt{D_T/(k_T + q_{VL})}$.

The solution of equation (16) with boundary conditions $\Gamma(0) = \Gamma_1$, $\Gamma(1) = \Gamma_2$ is:

$$\Gamma(\xi) = \Gamma_1\frac{\sinh(\Psi(1-\xi))}{\sinh(\Psi)}\exp\left(\frac{Pe_T\xi}{2}\right) + \Gamma_2\frac{\sinh(\Psi\xi)}{\sinh(\Psi)}, \tag{17}$$

where $\Psi = \sqrt{(Pe_T/2)^2 + \Phi^2}$. For boundary conditions of the form $\Gamma(0) = \Gamma_1$, $\Gamma'(1) = 0$, the solution is as follows:

$$\Gamma(\xi) = \Gamma_1\frac{\Psi\cosh(\Psi(1-\xi)) + (Pe_T/2)\sinh(\Psi(1-\xi))}{\Psi\cosh(\Psi) + (Pe_T/2)\sinh(\Psi)} \times \exp\left(\frac{Pe_T\xi}{2}\right). \tag{18}$$

The typical boundary condition at $z = 0$ is $C_T(0) = C_D$, and therefore in the following $\Gamma_1 = \Gamma(0) = 1$; a more general condition was formulated in (Patlak and Fenstermacher, 1975).

If the tissue layer is enough wide that the solute concentration deep within the tissue is in equilibrium with blood, $C_T(1) = \kappa C_B$, i.e. $\Gamma_2 = \Gamma(1) = 0$, then normalized concentration gradient is described by the following exponential function, c.f. (Patlak and Fenstermacher, 1975):

$$\Gamma(\xi) = \exp\left(-\left(\Psi - \frac{Pe_T}{2}\right)\xi\right). \tag{19}$$

Because $\Psi \geq Pe_T/2$, equation (19) describes the exponential decrease of the normalized concentration gradient, Γ. Equation (19) may be derived from equations (17) and (18) for $\Psi \gg 1$ and $\Gamma_2 = 0$.

4. TRANSPORT PARAMETERS

For the typical values of the transport parameters and physiological conditions within the tissue (e.g., the muscle) one may describe the capillary wall using large pores of 310 Å radius, and small pores of 65 Å radius (Rippe and Haraldsson, 1994). It is assumed that large pores form 0.5 % of the total pore area. The lumped parameter $A_0/\Delta x$, where A_0 is the total pore area, is assumed to be equal to 110 cm per 1 g of tissue. The calculated net hydraulic permeability for both pore systems of the capillary wall, c.f. equation (4), is $L_{PC}a_C$ =0.000073 ml/min/mmHg/g, with 0.1 of the net value attributed to large pores, and 0.9 of the net value to small pores. For hydrostatic pressure gradient between blood and interstitial fluid of 15.3 mmHg, the oncotic blood pressure 22.88 mmHg and the oncotic pressure of interstitial fluid 9.15 mmHg, the fluid flow through the large pores is 0.000106 ml/min/g, and through the small pores 0.000167 ml/min/g. Thus, the absorption flow, q_{VL}, is

equal to the total fluid flow through the capillary wall: q_{VL} = 0.000273 ml/min/g.

Transport parameters for solutes depend on their Stokes radius. The solute diffusivity in water, D_W, is also related to the Stokes radius by the Einstein formula (with some corrections, as the measured values of D_W for proteins are about 0.7 of the values calculated from the Stokes radius). Diffusive permeability and sieving coefficient for different solutes transported through the capillary wall may therefore be calculated using equations (2) and (3). Using the values of the transport parameters and the fluid flow rates one may calculate the ratio of the equilibrium solute concentration in the interstitial fluid to its concentration in blood, κ. For small solutes, of molecular weight less than 1000 daltons, κ is practically 1, for β_2-microglobulin $\kappa = 0.986$, for albumin $\kappa = 0.660$, and for IgM $\kappa = 0.212$.

The unidirectional clearances for the transport from blood to tissue, k_B, calculated according to the two pore model for the above values of the parameters are compared to the experimental data in Figure 1.

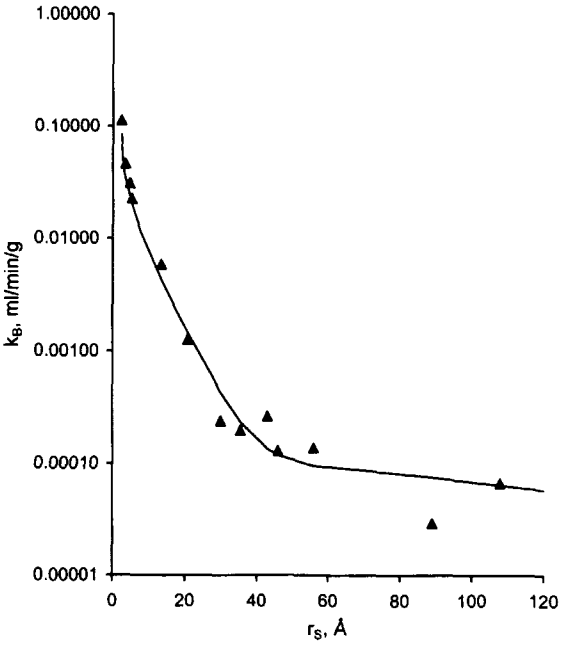

FIGURE 1 Unidirectional clearance (per unit tissue volume), k_B, for blood-to-tissue transport of solutes. - - theoretical values calculated using equation (8) and the values of parameters described in Section 4, ▲ – experimental values (Renkin, 1977)

The information about the transport parameters for the tissue, S_T and D_T, is scarce. Sieving coefficient, S_T, may be assumed to be 1 for most solutes of interest. For small solutes (up to 1000 MW) D_T is assumed to be 5.3 % of the solute diffusivity in water, D_W, and for larger solutes 5% of D_W. These are crude estimations, but they are in agreement with the available data (Dedrick et al, 1982; Flessner et al, 1997).

5. SOLUTE PENETRATION WITHIN THE TISSUE

Using the real distance from the tissue surface, x, equation (19) may be rewritten as:

$$\Gamma(x) \cong \exp(-x/\Lambda) \qquad (20)$$

with the characteristic value for the solute penetration to the tissue $\Lambda = L / (\Psi - Pe_T / 2)$. Λ has the unit of length and describes the rate of decrease of the normalized concentration gradient with increasing x, equation (19), in the case of $\Lambda \ll L$. The parameter Λ may be expressed as a function of two other parameters, Λ_D, which describes the penetration depth for purely diffusive transport, and Λ_C, which describes the penetration depth for purely convective transport.

If in equation (14) $j_{VT} = 0$, then the solution of the reduced equation for the boundary conditions $\Gamma(0) = 1$, $\Gamma'(1)=0$ is:

$$\Gamma(\xi) = \frac{\cosh(\Phi(1-\xi))}{\cosh(\Phi)}, \qquad (21)$$

c.f. (Leypoldt and Henderson, 1992). Note that $\Phi = L/\Lambda_D$, where $\Lambda_D = \sqrt{D_T/(k_T + q_{VL})}$, and $\Gamma(x) = \exp(-x/\Lambda_D)$ for $\Lambda_D \ll L$. Thus, Λ_D is the penetration depth for the purely diffusive transport of the solute to the tissue. On the other hand, if in equation (14) $D_T = 0$ and $j_{VT} > 0$, then the solution of the reduced equation for the boundary condition $\Gamma(0) = 1$ is:

$$\Gamma(x) = \exp(-x/\Lambda_C), \qquad (22)$$

where $\Lambda_C = S_T j_{VT}/(k_T+q_{VL})$ is the penetration depth for the purely convective transport of the solute to the tissue.

TABLE I Penetration depth for different transport processes

Solute	Λ_D, *mm*	Λ_C, *mm*	Λ, *mm*
Creatinine	0.25	0.03	0.26
Inulin	0.29	0.19	0.40
β_2-m	0.60	0.85	1.15
Albumin	0.71	2.63	2 81
IgM	0.44	3.40	3.46

The definition of Pe_T, equation (16), yields that $Pe_T = L\Lambda_C/\Lambda_D^2$. Therefore, using the definition of the net penetration depth for the combined diffusive and convective transport as $\Lambda = L/(\Psi\text{-}Pe_T/2)$, c.f. equation (19), one may write the following formula for Λ:

$$\Lambda = \frac{\Lambda_D}{\sqrt{1 + r^2/4} - r/2}, \tag{23}$$

where $r = \Lambda_C/\Lambda_D$. For $|r| \ll 1$, $\Lambda \approx \Lambda_D + \Lambda_C/2$, whereas for $r \gg 1$, $\Lambda \approx \Lambda_C$, and for $r \ll -1$: $\Lambda \approx 0$.

The penetration depths, Λ, Λ_D, and Λ_C, estimated using the presented above values of the transport parameters for a few solutes of clinical interest are shown in Table I.

Penetration depth for small solutes (creatinine) is dominated by the process of diffusion, for middle molecules (inulin, β_2-microglobulin) both processes contribute to the depth of solute penetration to the tissue, and for macromolecules (albumin, IgM) the convective transport prevails.

6. PHENOMENOLOGICAL VERSUS PHYSIOLOGICAL DESCRIPTION OF SOLUTE TRANSPORT IN PERITONEAL DIALYSIS

In the commonly applied phenomenological membrane model the following equation is assumed for the solute flux from dialysate to blood (Spiegler and Kedem, 1966; Lysaght and Farrell, 1989; Waniewski, 1994):

$$j_S = k_{BD}(C_D - C_B) + Sj_V[(1 - F)C_D + FC_B], \tag{24}$$

where k_{BD} is diffusive mass transport coefficient (expressed per unit surface area), S is sieving coefficient, j_V is fluid flux between blood and dialysate, and F is a weighing factor for the mean value of C_B and C_D. Various expressions for F were used, with:

$$F = \frac{1}{Pe} - \frac{1}{\exp(Pe) - 1}, \tag{25}$$

where $Pe = Sj_V/k_{BD}$, as for a homogenous membrane between two well mixed compartments (Spiegler and Kedem, 1966; Lysaght and Farrell, 1989; Waniewski, 1994), $F = 0$ (Lysaght and Farrell, 1989; Waniewski et al, 1992, 1995; Waniewski, 1994) or $F = 0.5$ (Spiegler and Kedem, 1966; Lysaght and Farrell, 1989; Waniewski et al, 1992; Waniewski, 1994).

In the distributed model the solute flux from the peritoneal cavity to the tissue is defined as:

$$j_S = j_{ST}(0) = -D_T \left.\frac{dC_T}{dx}\right|_{x=0} + Sj_{VT}C_T(0). \tag{26}$$

For the approximated solution given in equation (20), equation (26) may be presented as:

$$j_S = \frac{D_T}{\Lambda}(C_D - \kappa C_B) + Sj_{VT}C_D, \tag{27}$$

or, after rearranging its terms to the form similar to equation (24):

$$j_S = k_{BD}(C_D - \kappa C_B) + Sj_V[(1 - F)C_D + F\kappa C_B], \tag{28}$$

where $j_V = j_{VT}$, $S = S_T$, and

$$k_{BD} = \sqrt{D_T(k_T + q_{VL})}, \tag{29}$$

$$F = 0.5 - \alpha, \tag{30}$$

$$\alpha = \frac{\sqrt{1 + \frac{Pe^2}{4}} - 1}{Pe}, \tag{31}$$

with $Pe = \dfrac{\Lambda_C}{\Lambda_D} = \dfrac{Sj_V}{k_{BD}}$ (= r, see formula (23)). Note that Pe is the same in formulae (25) and (31). The comparison of the functions $F(Pe)$ provided by the distributed model and by the theory for homogeneous permselective membranes is shown in Figure 2. Approximated expressions for $F(Pe)$ in the distributed model are: (1) $\alpha \approx Pe/8$, i.e. $F \approx 0.5 - Pe/8$, for $|Pe| << 1$, (2) $\alpha \approx 0.5$, i.e. $F \approx 0$, for $Pe >> 1$, and (3) $\alpha \approx -0.5$, i.e. $F \approx 1$, for $Pe << -1$.

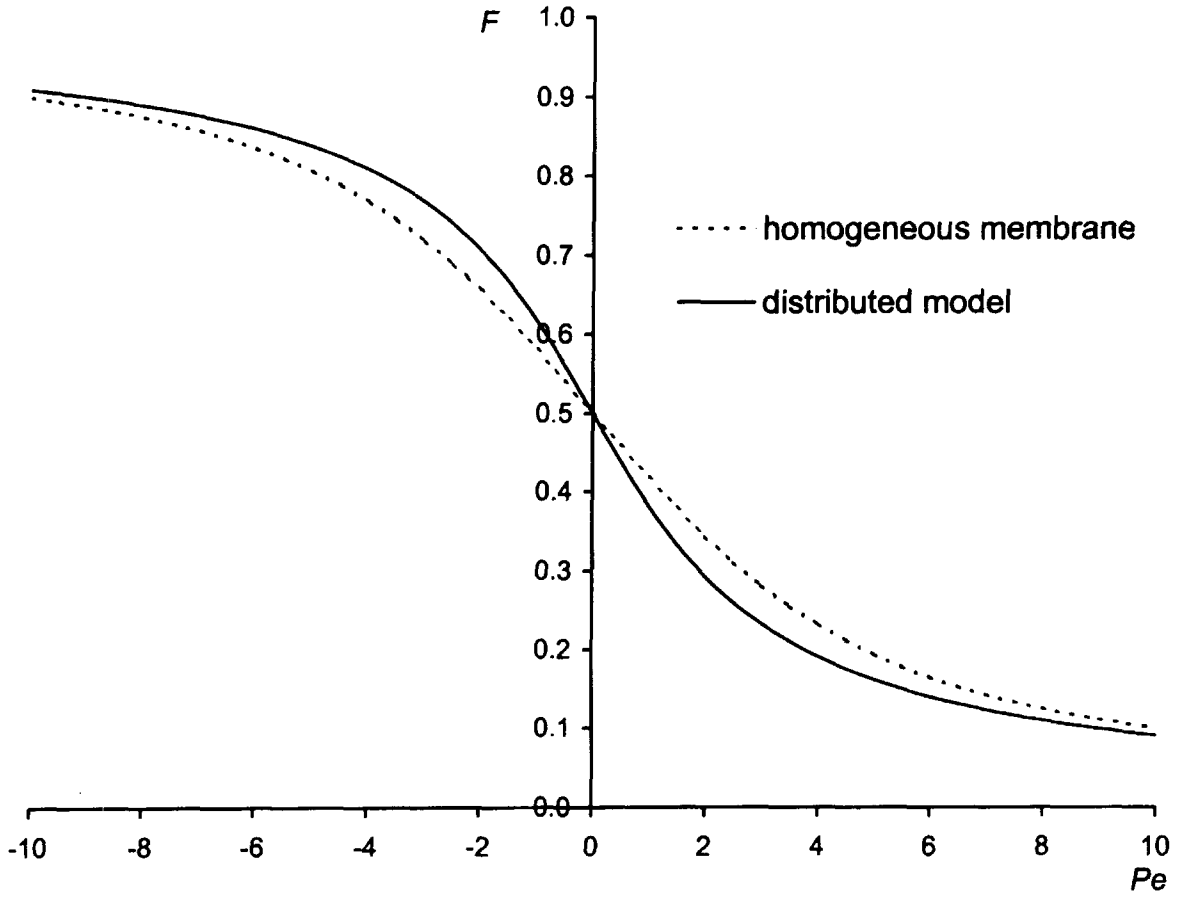

FIGURE 2 Weighing factor F for the mean membrane concentration as a function of Peclet number Pe. —— – calculated according to the distributed model, formula (30), ----- – calculated according the phenomenological model for homogeneous permselective membranes, formula (25)

The physiological interpretation of fluid flux j_V is different in both models. In the membrane model j_V is the flux of fluid between dialysis fluid and blood through an apparent membrane between them. In the distributed model j_V is the flux of fluid through the tissue. According to our simplified assumption j_V does not depended on x, i.e. the fluid is not absorbed from neither ultrafiltered to the tissue. However, what is usually measured in clinical and experimental dwell studies, is the change of the volume of dialysis fluid, and from these measurements the rate of fluid flow which crosses the surface of the tissue may be evaluated. Therefore the same value of j_V may be used in both models for the estimation of the transport parameters.

The important difference between equations (24) and (28) is the presence of coefficient κ in equation (28). In typical physiological conditions of the transport through the capillary wall κ is close to 1 for small and middle molecules, but substantially lower than 1 for macromolecules. Therefore, according to equation (28), the equilibration level for macromolecules in dialysate is not their concentration in blood, C_B, but their equilibrium concentration in the tissue $C_{Teq} = \kappa C_B$. In fact, the equilibrium level for total protein five times lower than blood concentration was observed in experiments in dogs with prolonged accumulation of the lost protein in dialysate (Rubin et al, 1985). Another consequence of the difference between both equations is the value of the estimated

sieving coefficient. Sieving coefficient may be measured directly if convective transport is prevailing, i.e. with very high fluid flow, or in isochratic conditions, i.e. during diffusive equilibrium at both sides of the membrane (Rubin et al, 1982; Park et al, 1995a). If the measurement is done using solute concentration in blood as the reference, then the obtained value depends on the direction of fluid flow. If $J_V > 0$ and $Pe \gg 1$, then the measured value of S is equal to S_T, whereas for $J_V < 0$ and $Pe \ll -1$ this value is equal to κS_T, c.f. equation (27). For high fluid flow through the capillary wall, κ may be lower than 1 even for small solutes. In contrast, the membrane model, equation (24), predicts the estimated values of S being independent of the fluid flow direction.

7. UNIDIRECTIONAL SOLUTE CLEARANCES IN PERITONEAL DIALYSIS

To evaluate the values of transport coefficients for peritoneal dialysis one may assume topographical homogeneity of the peritoneal tissue and calculate net solute flow as $J_S = A_M j_S$, where A_M is the total peritoneal surface area. In a similar way, net fluid flow may be calculated as $J_V = A_M j_V$, and net diffusive mass transport coefficient as $K_{BD} = A_M k_{BD}$. The typical total peritoneal surface area is assumed to be equal to 1 m^2 (Waniewski et al, 1999). The calculated values of K_{BD} are compared to the experimental ones in Figure 3. In general, there is quite good agreement between calculated K_{BD} and the measured values of the mass transport coefficient over a wide range of solute size (from urea, MW 60, to immunoglobulin M, MW 750 000). The measured transport coefficients for all solutes that are taken into account in Figure 3 can be explained by the combination of convective and diffusive transport between tissue and blood, convective transport by lymph, and purely diffusive transport across the tissue.

The curve in Figure 3 looks similar to the curve in Figure 1, which presents local transport coefficient k_B for the transport across the capillary wall. These two curves are not however identical. In Figure 4 the comparison of the two curves is shown, with both curves normalized so that the value of the respective coefficient for inulin ($r_S = 13.4$ Å) is equal to one. The difference is the result of the effect of the capillary distribution and tissue transport coefficients, which depend on solute size.

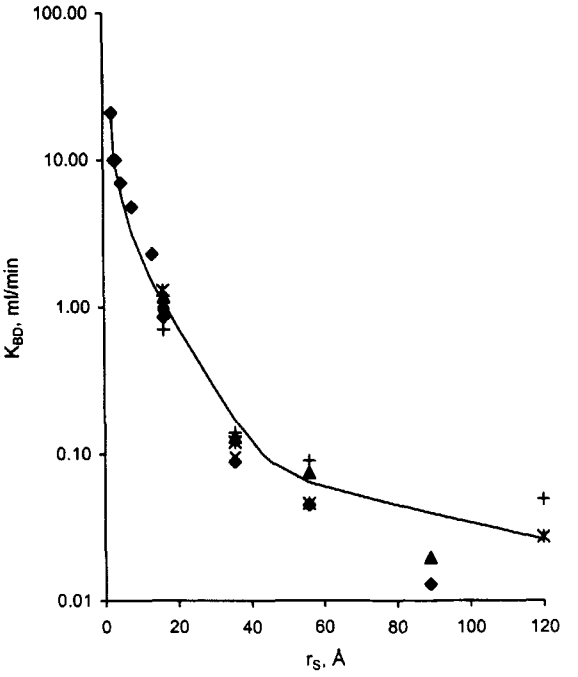

FIGURE 3 Unidirectional clearance with pure diffusion across the tissue, K_{BD}, for blood-to-dialysate transport during peritoneal dialysis. —— – theoretical values calculated using formula (29) for K_{BD} and peritoneal surface area A_M = 1 m^2, and the values of other parameters described in Section 4; * – experimental values from (Rippe and Stelin, 1989); + – experimental values from (Kagan et al, 1990); ▲ – experimental values from (Imholz et al, 1993); ♦ – experimental values from (Pannekeet et al, 1995)

In general, the combined diffusive – convective solute flow, J_S, may be described using unidirectional clearances $Cl_{D\to B}$ and $Cl_{B\to D}$ as follows (c.f. equation (28)):

$$J_S = Cl_{D\to B} C_D - Cl_{B\to D} C_B, \qquad (32)$$

where:

$$Cl_{D\to B} = K_{BD} + S J_V (1 - F), \qquad (33)$$

$$Cl_{B\to D} = \kappa (K_{BD} - S J_V F). \qquad (34)$$

Thus, unidirectional clearances comprise both transport components, diffusive and convective transport

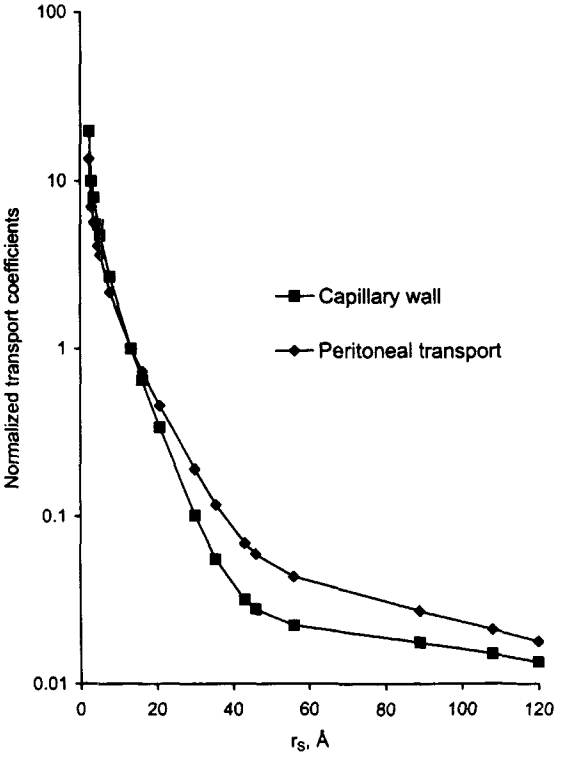

FIGURE 4 Comparison of theoretical curves from Figure 1 (k_B for the transport through the capillary wall) and Figure 3 (K_{BD} for the peritoneal transport from blood to dialysate). Both curves were normalized for the respective value for inulin (r_S = 13.4 Å)

through the tissue. They may be measured under some special conditions in experimental and clinical studies.

Theoretically evaluated values of $Cl_{D\to B}$ and $Cl_{B\to D}$ for the cases of 1) pure diffusion of solutes through the tissue, and 2) combined diffusive and convective transport through the tissue with J_V = 1 ml/min directed from dialysate to tissue, are shown in Figure 5. The value of J_V is a typical rate of fluid absorption from the peritoneal cavity to the tissue in clinical peritoneal dialysis (Heimbürger et al, 1995). Note that diffusive transport from dialysate to blood is enhanced by the fluid flow, whereas diffusive transport from blood to dialysate is directed against the fluid flow. The purely through-tissue diffusive clearance, $Df_{B\to D}$, was compared to the experimental data in Figure 3.

For small molecules (r_S < 10 Å) the four curves in Figure 5 are almost indistinguishable in agreement with the common observation that peritoneal diffusion of small molecules is not substantially influenced by low rate fluid flow. For middle molecules (10 < r_S < 20 Å) there is a small but measurable impact of convective transport on pure diffusive through – tissue clearances, as discussed in (Waniewski et al, 1994b), but the diffusive through – tissue clearances do not depend on the direction of diffusion ($Df_{B\to D} \approx Df_{D\to B}$). In contrast, all four curves are substantially different for macromolecules (r_S > 30 Å). $Df_{B\to D}$ curve reflects the typical values of macromolecules clearances measured in patients during routine peritoneal dialysis, c.f. Figure 3. These clearances may be interpreted according to the presented model as pure diffusive transport through the tissue.

In the case of dialysate-to-blood transport of macromolecules, as for example dextrans or radiolabelled albumin applied as volume marker, the rate of absorption of the marker from dialysate to tissue is about 1 – 1.5 ml/min, and this value corresponds with the combined diffusive and convective transport, $(Df+C)_{D\to B}$, with convective transport responsible for most of the clearance. The convective nature of the absorption of volume markers was well documented in clinical and experimental studies (Waniewski et al, 1994a). Note also the independence of the absorption rate on molecular mass of macromolecules shown by $(Df+C)_{D\to B}$ curve, which was found previously in peritoneal dialysis (Waniewski et al, 1994a). However, the same absorptive fluid flow should decrease the diffusive clearances of endogenous macromolecules transported from blood to dialysate, curve $(Df)_{B\to D}$ to the values shown in $(Df-C)_{B\to D}$ curve, i.e. by about 10 times. However, such low values of clearances of endogenous macromolecules are not observed. This paradoxical situation reflects one of the unsolved problems in physiological bases for peritoneal dialysis: the routes for transport of fluid and macromolecules in the tissue (see Discussion).

8. DISCUSSION

The basic ideas for the distributed modeling of the peritoneal transport were formulated by Dedrick,

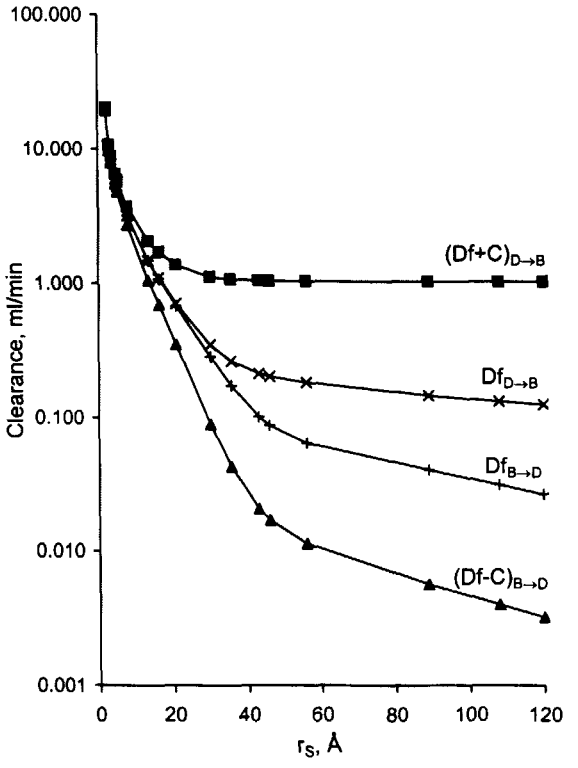

FIGURE 5 Theoretical values of unidirectional clearances during peritoneal dialysis, equations (33) and (34). —■— – $(Df + C)_{D\to B}$ – unidirectional clearance from dialysate to blood for combined diffusive (Df) and convective (C) transport through the tissue; —×— – $Df_{D\to B}$ – unidirectional clearance from dialysate to blood for pure diffusive transport through the tissue; —+— – $Df_{B\to D}$ – unidirectional clearance from blood to dialysate for pure diffusive transport through the tissue ($Df_{B\to D} = K_{BD}$, c.f. Figure 3); —▲— – $(Df - C)_{B\to D}$ – unidirectional clearance from blood to dialysate for diffusive transport (Df) across tissue to dialysate and fluid flow (C) through the tissue from dialysate

Flessner and colleagues (Dedrick et al, 1982; Flessner et al, 1984). The same approach was however discussed earlier for the exchange of gases between blood and artificial gas pockets within the body (Piiper et al, 1962) as well as in the general context of the exchange of matter and heat between blood and tissue for the intratissue source of solute or heat (Perl, 1962, 1963). The first application of the model for the description of the solute transport was proposed in (Patlak and Fenstermacher, 1975) for diffusion of small solutes from cerebrospinal fluid to the brain. The model was applied for analyses of the transport of small, middle and macro – molecules in studies of peritoneal dialysis in rats (Flessner et al, 1997; Flessner et al, 1985a-b) and in CAPD patients (Dedrick et al, 1982) as well as in studies on the transport of anticancer or other drugs applied intraperitoneally (Collins et al, 1982; Flessner and Dedrick, 1994), intravesically (Wientjes et al, 1991, 1993) or on skin (Gupta et al, 1995). Other applications included gas transport between subcutaneous or intraperitoneal gas pockets and blood (Piiper et al, 1962; van Liew, 1968; Collins, 1981). Some investigators applied the distributed model for the evaluation of diffusion combined with convective solute transport due to osmotically driven ultrafiltration from blood (Seames et al, 1990; Leypoldt and Henderson, 1992; Leypoldt, 1993), or included some reaction terms to describe the interaction of the solute with the tissue (Collins et al, 1982). Nevertheless, most of the applications of this modeling have dealt with purely diffusive solute transport. In contrast, peritoneal dialysis is an exceptional opportunity to study the combination of diffusive and convective transport of solutes over a wide range of solute size.

The presented here model combines the previous version of the distributed model (Dedrick et al, 1982; Flessner et al, 1984; Waniewski et al, 1999) with theoretical description of the capillary wall as a heteroporous membrane (Rippe and Haraldsson, 1994), and includes also lymphatic absorption of fluid and solutes from the tissue (Flessner, 1991; Flessner et al, 1997). In this way the most important factors, which contribute to the transport of solutes, are taken into account, and the transport of small, middle and macro – molecules may be considered within the unified approach. Diffusive transport prevails for small molecules, but the role of convective transport through the capillary wall and (convective) absorption with lymph increases with the increased molecular weight. For macromolecules, the model cannot ignore those two convective components. In particular, the blood – dialysate diffusive mass transport parameter, k_{BD}, depends on all the local transport parameters: blood – tissue diffusive transport coefficient, k_{BT}, sieving coefficients and fluid flow rates for small and large pores in the capillary wall, and lymphatic absorption

from the tissue, q_{VL}, see equation (29) and equations (5) – (9). Furthermore, all the local transport coefficients enter the formula for factor κ, c.f. equation (13).

For solutes, which diffuse very fast through the capillary wall, as lipophilic gases, or even some hydrophilic small molecules, as urea, the blood – tissue transport depends on the local rate of blood flow (perfusion). This phenomenon may be easily included into the model as described in (Waniewski et al, 1999).

The pore model was applied in the present study as a phenomenological description that can combine many physiological factors and structural characteristics concerning the transport of fluid and solutes through the capillary wall. In spite of an idealized description of the pore structure, the model was able to yield a useful description of many experimental data (Rippe and Haraldsson, 1994; Michael and Curry, 1999). Note however, that we use so called "structural" size of the pores, in contrast to "functional" size applied in the study of albumin transport (Rippe and Haraldsson, 1994). The application of the structural size of the pore in our modeling was necessary to provide a unified description of small and large molecules. However, any other description of the blood – tissue transport parameters may be also applied, including any raw experimental values for solutes of interest.

The analytical solutions for the concentration profiles within the tissue were obtained assuming the steady state of the transport processes, uniform structure of the tissue and the transport parameters independent of the solutes concentrations. The two last assumptions should be considered as simplification, because the structure of the interstitium as well as the physiological state of the capillary bed of the living tissue may change after disturbance induced by dialysis fluid (Waniewski et al, 1999; Zakaria et al, 1999a-b). Nevertheless, the theory presented here may be considered as valid for small perturbations of the state of tissue.

The steady state of the solute transport may be reached in some special experimental conditions, as shown by the results of the above cited studies, but for peritoneal dialysis the necessary conditions are fulfilled only approximately. Nevertheless, this assumption is commonly applied for the estimation of the transport parameters on the base that the rates of the solute concentration change in dialysate and blood are rather low for most solutes of clinical interest.

Convective transport through the tissue was assumed unidirectional and constant in time and space. This is also an approximation that allows us to omit the problem of the source of the fluid and the changes of the fluid flow rate due to contribution of blood – tissue and lymphatic fluid flows. In particular, fluid entering the tissue because of high hydrostatic pressure in the peritoneal cavity is absorbed to blood and lymph, and its flow rate decreases with the distance from the surface. On the other hand, blood is the source of fluid flow to the peritoneal cavity, which is induced by high crystalloid osmotic pressure of dialysate exerted by osmotic agents, as glucose, amino acids, etc. The agents are transported into the tissue mainly by diffusion, and their concentration in the tissue, and therefore their osmotic effectiveness, decreases with the distance from the tissue surface. Again, the rate of induced fluid flow changes in space. In standard peritoneal dialysis this rate depends also on time. Therefore, the assumption of the constant fluid flow restricts our results to be approximately valid only in some special experimental conditions. Nevertheless, the qualitative insight provided by the model is in agreement with many experimental and clinical observations. Further theoretical investigations, which must be based on numerical solutions of coupled partial differential equations for fluid and major osmotically active solutes, will probably provide quantitatively refined, but qualitatively similar results.

Strictly speaking, the applied description of the fluid flow assumes the flow through the whole tissue width, i.e. the flow that crosses both surfaces of the tissue layer. Such assumptions need not be applicable to many organs involved in peritoneal dialysis. However, most of the results were obtained in the current study for the case of the equilibration of the solute with blood deep within the tissue, i.e. for penetration depth smaller than the tissue width. In this case the

details of the boundary conditions on the surface other than that in contact with dialysis fluid may not affect substantially the distribution of the solute within the tissue.

As noted above, in peritoneal dialysis two fluid flows in opposite directions are observed to operate at the same time. The first one is directed from dialysate to tissue and induced by increased hydrostatic pressure in the peritoneal cavity after instillation of dialysis fluid. The other is directed from blood capillaries to the peritoneal cavity, and is induced by high concentration of osmotic agent in dialysis fluid (and in the tissue). How these two flows can coexist in the interstitium and in the layer of mesothelial cells, which covers the tissue surface, is not known. An interesting hypothesis suggests, that osmotically driven ultrafiltrate would come only from the superficial blood capillaries, which form rather loose network just under the surface of the tissue (Flessner et al, 1992; Carlsson, 1999). In contrast, the absorptive, driven by hydrostatic pressure in the peritoneal cavity, fluid flow would enter the tissue in "windows" between the superficial capillaries. If the hypothesis is proved, the tissue might be considered theoretically as the sum of two regions, and in each of them only one unidirectional fluid flow would exist (with rather complex situation at the border of the regions). Our model would (approximately) apply to each of the regions separately. However, no experimental evidence for or any theoretical quantitative analysis of the hypothesis exists so far.

Superficial capillaries might also be a source of some convective leak of macromolecules through the large pores directly to dialysate, as postulated by the pore model of the peritoneal membrane (Rippe and Stelin, 1989; Haraldsson, 1995; Krediet and Rippe, 1996). This would be the third fluid flow during peritoneal dialysis, driven mainly by hydrostatic pressure in blood capillaries, which is higher than hydrostatic pressure in the peritoneal cavity. The pore model of the peritoneal membrane attributes most of the transport rate of macromolecules larger than albumin to this route, with some convective – diffusive transport of albumin through small pores (Rippe and Stelin, 1989; Haraldsson, 1995; Krediet and Rippe, 1996). The model takes into account also transcellular pores, which were identified with aquaporin channels in the endothelial cell membrane, and are permeable only for water (Carlsson et al, 1996). At least half of the osmotic flow induced by low molecular weight osmotic agents, e.g. glucose, passes through the transcellular pores. This kind of pores may be also included in our model for the description of ultrafiltration caused by glucose or similar agents.

Combining our results about transport of macromolecules in peritoneal dialysis with the hypothesis about specific role of superficial blood capillaries, we may suggest that the main source of proteins in dialysate is superficial capillaries (by convective leakage), but some small amount can get to dialysate by diffusion against the absorptive fluid flow (curve $(\text{Df-C})_{B\to D}$ in Figure 5) in "windows" between superficial capillaries. However, the idea of prevailing convective transport of macromolecules is in disagreement with some experimental results. For example, it was shown that the addition of protein to dialysis fluid reduced their transport from blood to dialysate, what suggests their diffusive rather than convective transport (Leypoldt, 1993). Note also, that if the convective albumin transport was from superficial capillaries, then the oncotic pressure of albumin reach dialysate should counteract oncotic pressure of blood and result in immediate increased fluid and albumin transport through the small pores. In contrary, a delay in ultrafiltration was observed if dialysis fluid with albumin as osmotic agent was applied in rats (Park et al, 1995b). Furthermore, the leakage of proteins from the superficial capillaries directly to dialysate would result in immediate appearance of labelled proteins in dialysate after their infusion to blood, which is in disagreement with the observed delay in the transport of labelled proteins compared to endogeneous proteins in peritoneal dialysis (Bianchi et al, 1975). These observations suggest that most of protein molecules is transported through the interstitial layer, before getting from blood to dialysate.

The main conclusions from our model, which may be of interest for physiological investigations, are:

1. Solutes in dialysate equilibrate to their concentration in the tissue, not in blood as assumed in the standard membrane model. This observation is of special importantance for macromolecules, which have $\kappa < 1$ in physiological conditions, and for small and middle molecules if ultrafiltration from blood is high.
2. Sieving of solutes during ultrafiltration from blood occurs at the capillary wall; in particular, during isochratic experiments the decrease of solute concentration within the tissue is similar as in dialysate.
3. Phenomenological transport parameters used in the membrane model may differ if estimated for blood to dialysate vs. dialysate to blood direction, because they do not take into account factor κ.
4. The distributed model supports the application of the formula for the mean weighted intramembrane concentration of the solute in the convective component of the membrane model, equation (24). However, the formula for the weighing factor F yielded by the distributed model differs slightly from the formula yielded by thermodynamic theory of permselective membranes.

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