The present article provides a theoretical description of the changes of interstitial hydrostatic pressure, tissue hydration, and protein distribution in the tissue during a peritoneal dwell with isotonic fluid. The mathematical model is based on the concept of uniformly distributed capillary and lymphatic systems within a deformable, porous tissue. Protein transport was analyzed for diffusive and convective transport of serum albumin (SA) and radiolabeled albumin (RISA; added to dialysis fluid) using Darcy’s law for fluid flux through the tissue and the two-pore theory for water and protein flow across blood capillary walls.

Numerical results showed a local increase of interstitial hydrostatic pressure and tissue hydration over physiologic level in the tissue layer close to the peritoneal surface. The water inflow to the tissue displaced interstitial SA into the deeper tissue layers and yielded RISA accumulation in the tissue at a concentration locally higher than that in the dialysis fluid. The description of water flow agreed with clinical data, but yielded a higher-than-expected hydrostatic pressure in the deep tissue layers. The steady-state rates of fluid and RISA absorption from the peritoneal cavity, but not of SA clearance, agreed with the clinical data.

Key words
Water transport, interstitial hydrostatic pressure, tissue hydration, peritoneal absorption

Introduction
Increase in intraperitoneal pressure after infusion of dialysis fluid causes absorption of fluid and solutes from the peritoneal cavity to the tissue. Water flow plays the crucial role in this process, because water acts as a vehicle for solutes, which are transported by convection. The quantitative description of water absorption to the tissue requires application of a distributed model that takes into account the combined role of interstitium, blood capillaries, and lymphatics distributed within the tissue space surrounding the peritoneal cavity.

The theoretical model presented in this paper is focused on water and protein transport in the tissue during isotonic peritoneal dialysis. It is based on a previously developed model of peritoneal water absorption (1–3). The current model takes into account protein diffusion, hydrostatic pressure–driven convection, absorption from the tissue by the lymphatics, and exchange between the tissue and blood through the porous capillary wall described by the two-pore theory. Fluid flux through the tissue is described by Darcy’s law. Protein transport was analyzed for diffusive and convective transport of serum albumin (SA) and radiolabeled albumin (RISA; used as a volume marker) added to dialysis fluid.

Methods
The model presented here is based on equations for local volume and solute balance (1–3). The time evolution of the interstitial void volume, $\theta$, depends on the volumetric flux across the interstitium ($j_V$) and the rate of the net fluid flow ($q_V$) between the tissue and the blood capillaries and lymphatics. Moreover, $\theta$ is a function of the interstitial hydrostatic pressure $P$, as previously described (2). The transport of solutes, such as SA or RISA, depends on the solute flux across the interstitium ($j_m$) and the rate of the net solute exchange between tissue, blood, and lymph ($q_m$), where index $m$ denotes either SA or RISA.
Transport of water and solutes across tissue

The volumetric flux, \( j_V \), is described using Darcy’s law,

\[
    j_V = -K \frac{\partial P}{\partial x}, \tag{1}
\]

where the tissue hydraulic conductivity, \( K \), is a function of the local hydrostatic pressure \( P \) \( (2) \). The solute flux, \( j_m \), is described as

\[
    j_m = -D_{\text{eff}} \frac{\partial C_m}{\partial x} + j_V \cdot C_m, \tag{2}
\]

where \( C_m \) is the local solute concentration in the tissue, \( D_{\text{eff}} \) is the effective tissue diffusivity for the solute molecule, and \( m \) denotes either SA or RISA.

Transendothelial and lymphatic transport of water and solutes

The fluid exchange between blood and tissue, \( q_V \), is described as

\[
    q_V = L \alpha (P_B - P) - L \alpha s_\Pi (P_B - P) - q_{\text{lymph}}, \tag{3}
\]

where \( L \alpha \) is the capillary wall hydraulic conductance, \( s_\Pi \) is the capillary wall reflection coefficient, \( P_B \) and \( P \) are the blood hydrostatic and oncotic pressure respectively, \( \Pi \) is the interstitial fluid oncotic pressure, and \( q_{\text{lymph}} \) is the rate of lymphatic absorption from the tissue. Using albumin as a representative protein, \( L \alpha \) and \( s_\Pi \) are calculated according to the two-pore theory \( (4) \).

The change in the interstitial oncotic pressure, \( \Pi \), is described by

\[
    \Pi = (\Pi_0 / C_{0,SA}) \cdot C_{SA}(t,x), \tag{4}
\]

where \( \Pi_0 \) is the initial tissue oncotic pressure and \( C_{0,SA} \) is the initial tissue concentration of SA. The rate of the net solute flow to the tissue, \( q_m \), can be calculated according to the two-pore model as a sum of the net solute flow through the small \( (q_{mS}) \) and the large \( (q_{mL}) \) pores, reduced by the solute lymphatic absorption from the tissue \( q_{m \text{lymph}} \).

We assume also that the lymph flow is a function of interstitial pressure \( (1,2) \), given by

\[
    q_{\text{lymph}} = q_{L0} + q_{L1}(P - P_0). \tag{5}
\]

Initial and boundary conditions

Initial hydrostatic pressure in the interstitial fluid is assumed to be 0 \( [P(0,x) = P_0 = 0] \)—that is, the tissue is in equilibrium before the infusion of fluid into the peritoneal cavity.

After infusion, the hydrostatic pressure of the interstitial fluid at the peritoneal surface is equal to the hydrostatic pressure in the peritoneal cavity \( P_D \) \( [P(t,0) = P_D] \), whereas at the external surface of the tissue (that is, for \( x = x_{\text{MAX}} \)): \( \partial P / \partial x = 0 \), which means that the external surface (for example, the skin) is impermeable to water \([j_V(t,x_{\text{MAX}}) = 0]\). The initial concentration of SA in the tissue is constant and equal to its physiologic value, but the initial RISA concentration in the tissue is 0. At the peritoneal surface, the SA concentration is the same as that in the dialysis fluid (that is, 0), but the RISA concentration is equal to its concentration in the dialysis fluid. The external surface is assumed to be impermeable to proteins (for example, the skin of the abdominal wall muscle). In dialysis fluid and blood, the \( P_D, P_B \), and SA and RISA concentrations are assumed to be constant during the simulated dwell time.

Transport parameters for peritoneal dialysis

Total water absorption from the peritoneal cavity to the tissue \( (J^V) \) can be calculated as

\[
    J^V(t) = j_V(t,0) \cdot A, \tag{6}
\]

where \( A = 0.5 \text{ m}^2 \) \( (2) \). The clearance of SA \( (Cl_{SA}) \) can also be calculated from the distributed model as

\[
    Cl_{SA}(t) = -\frac{j_{SA}(t,0) \cdot A}{C_{B,SA}}, \tag{7}
\]

where \( C_{B,SA} \) is the SA concentration in blood. Peritoneal diffusive mass transport coefficients, \( K_{BD} \), for small solutes and albumin were calculated as previously described \( (5,6) \).

Results

Computer simulations of water and solute transport were performed for \( x_{\text{MAX}} = 1 \text{ cm}, P_D = 7 \text{ mmHg}, P_B = 11.6 \text{ mmHg}, \Pi_0 = 11.2 \text{ mmHg} \), fraction of tissue volume available for albumin transport = 0.50 \( (3) \), \( C_{B,SA} = 0.04 \text{ g/mL}, C_{0,SA} = 0.6C_{B,SA} \) \( (7) \), and
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\(D_{\text{eff}} = 0.46 \cdot 10^{-7} \text{ cm}^2/\text{s}\) for albumin and \(2.92 \cdot 10^{-6} \text{ cm}^2/\text{s}\) for creatinine. The parameters for pore theory, including \(P_b = 22.88 \text{ mmHg}\), \(A_0 / \Delta x = 110 \text{ cm/g tissue}\), \(\alpha_S = 0.929\), \(\alpha_L = 0.056\), and \(\alpha_C = 0.015\) were taken from (4,6,8). All remaining parameters have previously been described (2).

Water transport and interstitial pressure distribution
Fluid infusion into the peritoneal cavity increases intraperitoneal pressure and causes an inflow of water into the surrounding tissue. This inflow results in an increase of hydrostatic pressure in the tissue, especially close to the peritoneal surface, but a substantial drop in \(P\) in the tissue as the distance from the peritoneal surface increases (Figure 1). Fluid flows from the cavity to the tissue and expands the void volume in tissue layers close to the cavity, progressing deeper into the tissue (Figure 1). The thickness of the tissue layer that is fully filled up with water is, in the steady state, about 0.4 cm. Moreover, hydration in the deeper tissue layer is 78% higher than it is in physiologic equilibrium. Water flux across the tissue decreases with dwell time and distance from the peritoneal cavity (not shown).

The time needed to obtain stabilization of the \(J_N^{IN}\) defined here, is the time after which the change in the \(J_N^{IN}\) for each \(x\) is less than 10% of the final value of \(J_N^{IN}\) — in this case, 235 minutes for the first fluid infusion. However, this value decreases to less than 30 minutes in the calculations for consecutive dialysis fluid exchanges, as shown in previous simulations (2). Furthermore, the total fluid absorption from the peritoneal cavity to the tissue at the steady state is equal to 1.81 mL/min, and may be compared to lymphatic absorption from the tissue in physiologic equilibrium, that is, \(q_{L0} \cdot A \cdot x_{\text{MAX}} = 0.13\) mL/min. After reaching a

\[\text{FIGURE 1} \quad \text{Interstitial hydrostatic pressure, } P \text{ (left upper panel); void volume, } q \text{ (right upper panel); serum albumin concentration, } C_{SA} \text{ (left bottom panel); and labeled albumin concentration, } C_{\text{RISA}} \text{ (right bottom panel), during peritoneal dialysis at various times, } t, \text{ as a function of distance } x \text{ from the peritoneal surface. The period (time step) between the profiles is 25 minutes. The bold dashed line depicts the distribution 5 minutes after infusion; the bold solid line depicts the final pressure profile in the tissue.}\]
new steady state during dialysis, 77% of the total water absorption from the tissue goes to the blood capillaries through the small pores, but water still passes to the tissue through the large pores. The rest of the fluid (23%) is absorbed by the lymphatics situated in the tissue.

Endogenous protein transport
Initially, a transient increase of SA concentration in the middle layer of the tissue, caused by protein-free water from the peritoneal cavity that displaces SA from the subperitoneal layer of the tissue can be observed (Figure 1). Later, the peak in SA concentration moves toward the deeper tissue layers and gradually disappears because of diffusion and absorption of SA from the tissue and inflow of protein-free water from the peritoneal cavity. The final SA concentration changes with distance, from a very low value close to the peritoneal surface to a level higher than the physiologic level in the deeper part of the tissue (Figure 1).

Clearance of albumin calculated at the steady state is \( C_{\text{SA}} \) = 0.0003 mL/min. Furthermore, the net albumin absorption from the tissue occurs mainly through the lymphatics distributed in the tissue, but large pores play essential role in the net albumin inflow to the tissue. Moreover, at the steady state, a small amount of SA is also absorbed through the small pores. However, this latter transport is highly restricted because of the effect of albumin sieving (sieving coefficient: about 0.04) in the small pores.

Volume marker transport
The water flow transports marker molecules from the peritoneal cavity into the tissue, causing RISA accumulation in the interstitium (Figure 1). According to the model, RISA has two pathways by which to leave the tissue: it can be absorbed either by the lymphatics or through the blood capillary wall. However, the constant inflow of water into the tissue through the large pores and the sieving effect of the small pores results in the practical reality that RISA can be absorbed from the tissue only by the lymphatics.

Diffusive mass transfer coefficients for creatinine and albumin
The diffusive mass transfer coefficient for creatinine, \( K_{\text{BD,creat}} \) was 7.9 mL/min, and the diffusive mass transfer coefficient for SA was \( K_{\text{BD,SA}} \) = 0.05 mL/min.

Discussion
The interstitial pressure distribution in the tissue after infusion of isotonic solution was measured in the rat abdominal wall (9). The measured steady-state pressure profiles decreased with distance from the peritoneal surface of the tissue, as seen in the present study as well as in previous computer simulations for the experimental data in rats and humans (1,2). However, positive pressure values at the external surface are higher in the computer simulations than are observed in experimental studies. The basic level of lymphatic absorption from the tissue was within the range 2.6\( \times \)10\(^{-5} \) – 2.9\( \times \)10\(^{-5} \) mL min\(^{-1} \) g\(^{-1} \), which is considered typical for human physiology (10), and the total fluid absorption from the peritoneal cavity to the tissue at the steady state, \( J_{V} \), was only slightly higher than that measured in clinical studies \([0.8 – 1.5 \text{ mL/min (2)}]\).

The effect of RISA accumulation has been reported previously by others (11,12). The modeled profiles of the accumulated RISA in the tissue do not agree with the experimental data in rats (13,14); however, similar profiles were obtained in a theoretical study of absorption of radiolabeled immunoglobulin G (15). The decrease in oncotic pressure in the peritoneum during dialysis, concomitant with the unchanged oncotic pressure in the subcutaneous layer, is in qualitative agreement with our calculation of the SA concentration in the tissue (16). According to our results, the transient wave of the increased protein concentration obtained in the simulations lasted for about 1 hour. However, at present, no experimental data are available to verify this finding. The clearance of serum albumin, \( C_{\text{SA}} \) = 0.0003 mL/min calculated at the steady state, is far below clinical values \([0.05 – 0.1 \text{ mL/min (17)}]\), and that result agrees with previous theoretical studies about protein transport against the direction of water flow (6,18). Conversely, the values of the diffusive mass transfer coefficients for small solutes such as creatinine are in line with the clinical data \((7.5 – 9.5 \text{ mL/min})\).

Conclusions
Our model correctly predicts some water and protein transport characteristics, but the modeled rate of leakage of serum albumin to the peritoneal cavity was considerably lower than that reported in clinical studies. This discrepancy suggests that albumin leakage must be described by a mechanism not included in
the current version of the model. For example, the liver may be the source of most of the albumin. Because the liver is an internal organ, the pressure gradients are unlikely to be effective in setting up convection into the parenchyma.

References


Corresponding author: Joanna Stachowska–Pietka, Institute of Biocybernetics and Biomedical Engineering, Polish Academy of Sciences, ul. Trojdena 4, Warsaw 02-109 Poland.
E-mail: joannas@ibib.waw.pl