A Mathematical Model of Peritoneal Fluid Absorption in Tissue

Joanna Stachowska–Pietka, Jacek Waniewski, Michael F. Flessner, Bengt Lindholm

To investigate how water flow and interstitial pressure change in tissue during a peritoneal dwell with isotonic fluid, we developed a mathematical model of water transport in the tissue. Transport through muscle alone (M) and through muscle with intact skin (MS) were considered for the rat abdominal wall, using various parameters for muscle and skin. Based on the concept of distributed capillary and lymphatic systems, two main transport barriers were taken into account: capillary membrane and interstitium. We calculated the tissue hydrostatic pressure profiles and compared them with experimental data.

The theoretic steady-state pressure distribution for model M is in good agreement with the experimental data. In model MS, the theoretic distribution diverges from the data in the subcutaneous layer. The transient times for fluid flow in the tissue for both model simulations are rather long (40 minutes in model M and 95 minutes in model MS) and depend on intraperitoneal pressure. The fraction of fluid absorbed from the tissue by the lymphatics increases with time from 10% to 97% of fluid flow from the peritoneal cavity.

Key words
Distributed model, water transport, interstitial hydrostatic pressure, void volume

Introduction
The infusion of dialysis fluid into the peritoneal cavity increases intraperitoneal hydrostatic pressure and, in consequence, causes water and solutes to flow into and through the tissues surrounding the cavity. It is clinically observed that absorption of water from the peritoneal cavity into tissue—which makes up about 70% – 80% of total peritoneal absorption—substantially reduces net ultrafiltration in peritoneal dialysis patients (1). To evaluate the rate of water absorption to tissue, the roles of the interstitium, the blood capillary wall, and the lymphatics in the fluid exchange within the tissue must be considered.

During a peritoneal dialysis exchange, fluid encounters two main resistances: the capillary wall and the interstitium. Starling forces determine exchange through the blood capillary wall. Transport through the tissue is assumed to follow the Darcy law. Transport parameters such as interstitial void volume, interstitial hydraulic conductivity, and lymphatic absorption in tissue depend on the interstitial hydrostatic pressure, as demonstrated by experimental data (2–5).

In the present study, we aimed to provide a theoretic model of water flow and hydrostatic pressure distribution in tissue. The model was developed to demonstrate the variation in interstitial pressure and water flow with time. To compare model predictions with data from animal experiments, two cases were considered:

- Model M described a muscle layer without skin—that is, the tissue was permeable for fluid flow at both surfaces
- Model MS examined skeletal muscle with subcutaneous and skin layers—that is, the tissue was permeable at the peritoneal surface only (6)

Based on the theoretical results from models M and MS, we evaluated the influence of Starling forces on the total water absorption in tissue and on the fractions of fluid absorbed directly to blood or to lymphatic vessels.

Methods
The distributed model of peritoneal transport is based on the assumption that blood and lymphatic...
capillaries are uniformly distributed within the tissue, and that interstitium is a deformable, porous medium (7,8). The void volume—that is, the fraction of the total tissue space that is available for interstitial water—changes because of the inflow of fluid from the peritoneal cavity. The time evolution of the void volume depends on the volumetric flux across the interstitium ($j_v$) and the rate of the net fluid flow ($q_L$) between tissue and blood capillaries and lymphatics. The equation for the interstitial void volume ($\theta$) change is

$$\frac{\partial \theta}{\partial t} = - (\partial / \partial x) j_v + q_V$$  \[1\]

where $t$ is time, $x$ is the distance measured from the peritoneal surface ($x_0$) to the external surface ($x_M$ in model M, $x_{MS}$ in model MS), and $x_0 < x_M < x_{MS}$. According to the Darcy law, volumetric flux across the interstitium depends on the local tissue pressure gradient and local tissue hydraulic conductivity ($K$) and is equal to $j_v = -K (\partial P / \partial x)$. The tissue hydraulic conductivity, $K$, is a function of local hydrostatic pressure $P$: $K = a_0$ for $P < b_0$, and $K = a_0 + a_1 (P - b_0)$ for $P \geq b_0$, where $a_0 = 0.15 \times 10^{-6}$ and $a_0 = 0.3 \times 10^{-6}$ mL·cm⁻²·s⁻¹·mmHg⁻¹, $a_1 = 0.093 \times 10^{-6}$ mL·cm⁻²·s⁻¹·mmHg⁻², $a_2 = 0.186 \times 10^{-6}$ mL·cm⁻²·s⁻¹·mmHg⁻², $a_3 = 1.2$ mmHg (4).

According to the Starling law, fluid exchange between blood capillaries, lymphatic vessels, and tissue is described as $q_L = L_p a (P_B - P) - L_p \sigma_{\Pi} (\Pi_B - \Pi) - q_L$, where $L_p a$ is the capillary wall hydraulic conductance; $P_B$ and $\Pi_B$ are blood hydrostatic and oncotic pressure respectively; $\sigma_{\Pi}$ is the capillary wall reflection coefficient; $\Pi$ is interstitial fluid oncotic pressure; and $q_L$ is the rate of lymphatic absorption from tissue. We assume that oncotic pressure in the tissue, $\Pi$, depends on the void volume $\theta$ and can be calculated as $\Pi = \Pi_0 \theta_0 / \theta$, where subscript 0 means the value of the function at time $t = 0$. This functional relationship describes the effect of the dilution of interstitial fluid attributable to the inflow of protein-free dialysis fluid and the expansion of the void volume. We also assume that the lymph flow is a function of interstitial pressure given by $q_L = q_{L0} + q_{L1} (P - P_0)$ (5,9–12). The rate of lymphatic absorption, $q_{L0}$, in the steady state of fluid transport ($P = P_0$ at $t = 0$), is $q_{L0} = L_p a (P_B - P_0 - \sigma_{\Pi} (\Pi_B - \Pi_0))$, whereas $q_{L1}$ is, according to (5), equal to $0.4 q_{L0}$ for $x < x_M$ (in muscle layer) and $q_{L1} = 1.95 q_{L0}$ for $x_M \leq x \leq x_{MS}$ (in skin layer). Interstitial void volume is a function of the hydrostatic pressure:

$$\theta = \theta_{\min} + \frac{\theta_{\max} - \theta_{\min}}{1 + \left(\frac{\theta_{\max} - \theta_{\min}}{\theta_{\max} - \theta_{\min}} - 1\right) e^{-\beta (P - P_0)},}$$

with parameters $\theta_{\min} = 0.17$, $\theta_0 = 0.175$, $\theta_{\max} = 0.35$ mL/g, $\beta = 1.7$ mmHg⁻¹, and $\theta_{\min} = 0.4$, $\theta_0 = 0.405$, $\theta_{\max} = 0.58$ mL/g, $\beta = 3.4$ mmHg⁻¹ for the muscle and skin layers respectively (3,13). Note that, because void volume $\theta$ depends on interstitial pressure $P$, $\partial \theta / \partial t = (\partial \theta / \partial P) \cdot (\partial P / \partial t)$, and equation 1 can be converted to the form

$$\left(\frac{\partial \theta / \partial P}{\partial P / \partial t}\right) = - (\partial / \partial x) j_v + q_V.$$  \[2\]

Equation [2] is a nonlinear partial differential equation with one variable $P(t, x)$, which is assumed to be equal to 0 at $t = 0$ $P(0, x) = P_0 = 0$—that is, the tissue is in equilibrium before the infusion of fluid into the peritoneal cavity. After infusion, the hydrostatic pressure at the peritoneal surface is equal to the hydrostatic pressure in the peritoneal cavity $P_D$ $P(t, 0) = P_D$. At the external surface of the tissue, $P(t, x_M)$ equals 0 in model M (6). In contrast, $\left(\partial P / \partial x\right)(t, x_{MS})$ equals 0 in model MS, which means that the skin surface is impermeable for water $j_v(t, x_{MS}) = 0$.

**Results**

All simulations were carried out assuming that $P_B = 15.3$ and $P_D = 5.56$, $\Pi_0 = 14$ and $\Pi_B = 22.88$ mmHg. $\sigma_{\Pi} = 0.84$, $L_p a = 1.22 \times 10^{-6}$ mL·g⁻¹·s⁻¹, mmHg⁻¹ and $L_p a = 2.44 \times 10^{-6}$ mL·g⁻¹·s⁻¹·mmHg⁻¹ in the muscle and skin layers respectively, and that $x_M = 0.2$ cm and $x_{MS} = 0.24$ cm (6,8). With those parameters, the steady-state lymphatic absorption, $q_{L0}$, in the muscle was $9.6 \times 10^{-6}$ mL·s⁻¹·g⁻¹—that is, 2–3 times higher than used in other theoretical studies on tissue fluid transport (8,14).

The values of tissue hydrostatic pressure change with time and with distance from the surface (Figure 1). The difference in the pressure profiles between model M and model MS is substantial. The time needed to obtain the steady state (solid curve) is shorter in model M (about 40 minutes) than in model MS (about 95 minutes; see Figure 1).
The fraction of the total volumetric flux across the mesothelium, which is absorbed in the tissue by lymphatic vessels (L), can be decomposed into the fraction that is absorbed in the muscle layer (LM) and the fraction that is absorbed in the skin layer (LS). (See Figure 2, right panel.) On the other hand, total fluid absorption in tissue can be presented as the net result of lymphatic and direct absorptions to the blood. (See Figure 2, left panel.) The fraction of the total flux across the peritoneal surface that is absorbed from the tissue by lymphatic vessels increases during the dwell from about 10% in both models to 39% in model M and 97% in model MS (Figure 2, left panel). The increase occurs in both layers, and the fraction stabilizes after about 34 minutes in model M and 70 minutes in model MS (Figure 2, right panel). In

![Hydrostatic pressure profiles during peritoneal dialysis at various times in models M (muscle alone, left panel) and MS (muscle with intact skin, right panel). The interval between time steps is 310 s. The solid line is the steady-state line. The dotted line describes the experimental data (6).](image)

![Left panel: Volumetric flux across the peritoneal surface (dashed line), lymphatic absorption from the tissue (dotted line), and total absorption in the tissue (solid line) as a function of time for model MS (muscle with intact skin). Right panel: The ratio of lymphatic absorption from the whole tissue (solid line), from the muscle (dashed line), and from the skin (dotted line) over water inflow across the mesothelium as a function of time for model MS.](image)
model MS, the net ultrafiltration from capillaries to tissue can be observed for about 67 minutes (Figure 2, left panel), but later changes to (slight) absorption to capillaries.

Discussion
Both models provide a good description of the experimental data in the muscle layer, where the steady-state profiles are close to the data (Figure 1). However, in model MS, a difference occurs between the data and the steady-state profile in the subcutaneous layer (Figure 1). Perhaps the model needs further sophistication, and other factors have to be taken into account.

For example, because of its role in the balance of osmotic and hydrostatic pressure in the interstitial fluid, hyaluronan transport could be included in the model. The process of washing-out hyaluronan from the muscle layer into the subcutaneous layer (and its accumulation there) was observed experimentally (3). Furthermore, edema may also change the local tissue elasticity and transport parameters in the subcutaneous layer. The micropipette-servo null method, which is used to experimentally determine tissue pressures, is technically very challenging and difficult to use to measure multiple pressure profiles versus time. The lack of agreement between the data and the steady-state profile may therefore also be caused by the fact that the tissue-pressure measurements were made before the steady state was obtained.

References

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