Peritoneal Kinetics and Anatomy
We investigated a distributed model for the transport of fluid and glucose that allows for the description of hydrostatic pressure, interstitial fluid void volume, and glucose profiles in the tissue. Computer simulations for conditions mimicking the initial minutes of a peritoneal dialysis dwell with 3.86% glucose demonstrated that the rate of fluid flow to the peritoneal cavity was sensitive mostly to the reflection coefficient for glucose in the capillary wall, $\sigma_{CG}$, whereas the hydrostatic pressure in deep tissue layers was sensitive to the reflection coefficient for glucose in the interstitium, $\sigma_{TG}$. For hydrostatic pressure in the peritoneal cavity equal to 12 mmHg, $\sigma_{CG} = 0.5$, $\sigma_{TG} = 0.005$, and other parameters taken from published physiologic data, the rate of ultrafiltration was about 9 mL/min. Glucose concentration and hydrostatic pressure in the tissue increased in a layer less than 2 mm from the peritoneal cavity; deeper layers were close to their equilibrium values. If a high-value osmotic coefficient for the capillary wall is assumed, the proposed model describes hydrostatic pressure and glucose profiles that agree with available data.

**Key words**
Water transport, hydrostatic pressure, fluid void volume, reflection coefficient

**Introduction**

Two methods (1,2) are available for analyzing osmotic water flow from blood into the peritoneal cavity as induced by a high concentration of glucose or another osmotic agent:

- a membrane model that estimates the osmotic conductance of the barrier for peritoneal transport, or
- a three-pore model that allows for separate estimation of the reflection coefficient and the hydraulic conductance.

These two methods have proved to be useful in providing information about transport characteristics in various groups of patients on peritoneal dialysis. Nevertheless, any realistic description of the anatomy of the peritoneal transport system should include the capillaries, which are the source of water flow to the cavity, distributed within the tissue at a distance from the peritoneal surface (3).

The distributed modeling of solute transport yielded important insights into solute transport mechanisms in the tissue, but the distributed modeling of fluid flow has not been successful so far. The only study that included distributed modeling of ultrafiltration flow yielded a prediction of negative hydrostatic pressure inside the tissue, and that prediction was later disproved in experimental peritoneal dialysis in rats (4,5).

The objective of the present investigation was to formulate a distributed model of fluid transport that can predict the high rate of fluid flow observed in clinical studies and a non-negative hydrostatic pressure within the tissue.

**Materials and methods**

**Mathematical model**

The basic equation for the change in interstitial fluid volume fraction (fluid void volume), $\theta$, is

$$\frac{\partial \theta}{\partial t} = -\frac{\partial}{\partial x} (j_x) + q_x,$$

(1)
where \( j_p \) is the volumetric flux across the tissue; \( q_V \) is the rate of the net fluid flow to the tissue; \( x \) is the distance from the peritoneal surface through the tissue to the external tissue surface (for example, the skin), measured from \( x_0 = 0 \) cm to \( x_{\text{MAX}} \); and \( t \) is the dwell time (6,7).

The volumetric flux across the tissue is generated by the hydrostatic and osmotic pressure gradient and is described by the formula

\[
 j_V = -\theta K \left( \frac{\partial P}{\partial x} - \sigma_{TG} RT \frac{\partial C_G}{\partial x} \right),
\]

(2)

where \( P = P(t,x) \) is the local tissue pressure, \( C_G = C_G(t,x) \) is the local tissue glucose concentration, \( K \) is the hydraulic permeability of the tissue, \( R \) is the gas constant, \( T \) is the temperature, and \( \sigma_{TG} \) is the Staverman reflection coefficient for glucose in the tissue (6).

The fluid void volume, \( \theta \), is described as the following function of \( P \) (6,7):

\[
\theta = \theta_{\text{min}} + \frac{\theta_{\text{max}} - \theta_{\text{min}}}{1 + \left( \frac{\theta_{\text{max}} - \theta_{\text{min}}}{\theta_0 - \theta_{\text{min}}} \right) e^{-\beta(P-P_0)}}.
\]

(3)

The rate of fluid transport between blood and tissue, \( q_V \), is described as

\[
 q_V = q_V(P) = L_P a \sigma_{CG} RT (C_G - C_{GB}),
\]

(4)

where \( L_P a \) is the capillary wall hydraulic conductivity, \( C_{GB} \) is the glucose concentration in blood, and \( \sigma_{CG} \) is the Staverman reflection coefficient for glucose in the capillary wall (6). Note that equation 4 does not include the hydrostatic pressure differential across the capillary wall, because this difference is assumed to be balanced by the oncotic pressure difference and does not contribute to the net flow induced by a crystalloid osmotic pressure differential.

The local change in the glucose amount is given by the equation

\[
 \frac{\partial (\theta C_G)}{\partial t} = -\frac{\partial}{\partial x} \left( j_G \right) + q_G,
\]

(5)

where \( j_G \) is the glucose flux across the tissue and \( q_G \) is the rate of the net glucose flow to the tissue (6,8). The glucose void volume is assumed to be the same as the fluid void volume. The glucose flux across the tissue is composed of a diffusive component (proportional to the glucose concentration gradient in the tissue) and a convective component (proportional to glucose concentration and volumetric flux):

\[
 j_G = -\theta D_G \frac{\partial C_G}{\partial x} + s_{TG} j_V C_G,
\]

(6)

where \( D_G \) is the diffusivity of glucose in the interstitium \( (D_G = D_{\text{eff}} / \theta_0) \) and \( s_{TG} = 1 - \sigma_{TG} \) is the sieving coefficient of glucose in the tissue (6,8). The density of glucose flux from blood to tissue has a diffusive component (proportional to the difference of glucose concentration in blood and in tissue) and a convective component (proportional to the density of the volumetric flux from blood to the tissue):

\[
 q_G = p_G a (C_{GB} - C_G) + s_{CG} q_V [\theta (1 - F_G) C_{GB} + C_G F_G],
\]

(7)

where \( p_G a \) is the diffusive permeability of total capillary surface area per unit tissue volume, \( s_{CG} = 1 - \sigma_{CG} \) is the sieving coefficient for glucose in the capillary wall, and \( F_G \) is the weighting factor (6,8). The initial conditions are \( P(0,x) = P_0 = 0 \) and \( C_G(0,x) = C_{GB} = C_{GB} \) at \( t = 0 \), and the boundary conditions are \( P(t,0) = P_D \) and \( C_G(t,0) = C_{GD} \) at \( x_0 = 0 \), and \( (\partial P/\partial x)(t, x_{\text{MAX}}) = 0 \) and \( (\partial C_G/\partial x)(t, x_{\text{MAX}}) = 0 \) at \( x_{\text{MAX}} = L \), for all \( t \), where \( P_D \) and \( C_{GD} \) are hydrostatic pressure and glucose concentration in the peritoneal cavity respectively, and \( L \) is the width of the tissue layer. The boundary condition at \( x_0 = 0 \) means that the hydrostatic pressure and glucose concentration in the interstitial fluid at the peritoneal surface are the same as in dialysis fluid (\( P_D \) and \( C_{GD} \) respectively), and the boundary condition at \( x_{\text{MAX}} = L \) means that the other surface of the tissue is not permeable for fluid and glucose—for example, the skin of the abdominal wall muscle (6,8). The parameters \( P_D, P_D, C_{GD}, C_{GD} \) are constant during the simulated dwell time.

The ultrafiltration fluid flux to the peritoneal cavity, \( q_U \), is defined as the absolute value of the volumetric flow through the peritoneal surface, \( q_U(t) = |j_U(t,0)| \), and the ultrafiltration flow, \( Q_U \), as the ultrafiltration flux multiplied by the surface area of the contact between dialysis fluid and the tissue, \( A \), \( Q_U(t) = q_U(t) \cdot A \).
Computer simulations

The equations of the model were solved numerically for the following parameter values:

- \( K = 5.13 \times 10^{-5} \text{ cm}^2 \text{ min}^{-1} \text{ mmHg}^{-1} \)
- \( RT = 18.10^3 \text{ mmHg mmol}^{-1} \text{ mL} \)
- \( L_{\text{PD}} = 7.3 \times 10^{-5} \text{ mL min}^{-1} \text{ mmHg}^{-1} \text{ g}^{-1} \)
- \( p_{\text{GD}} = 3.4 \times 10^{-2} \text{ mL} \text{ min}^{-1} \text{ g}^{-1} \)
- \( D_G = 11.7 \times 10^{-5} \text{ cm}^2 \text{ min}^{-1} \)
- \( F_G = 0.5 \)

The parameters that describe function \( \theta \), equation 3, are given in (7). The boundary and initial values of hydrostatic pressure and glucose concentration are \( P_0 = 0 \); \( P_D = 3, 7, \) and 12 mmHg; \( C_{GB} = 6 \times 10^{-3} \text{ mmol mL}^{-1} \), \( C_{GD} = 180 \times 10^{-3} \text{ mmol mL}^{-1} \) (representing 3.86% glucose in dialysis fluid). The parameters \( \sigma_{CG} \) and \( \sigma_{CG} \) were varied to obtain \( \sigma_{jV} \) about –0.002 cm/min (meaning that \( Q_U \) is about 10 mL/min—that is, the typical ultrafiltration flow rate for 3.86% glucose solution, if the peritoneal surface in contact between the tissue and dialysis fluid, \( A \), is 5000 cm\(^2\) and \( P \) higher than or equal to 0 inside the tissue.

Figure 1 shows the results of computer simulations for \( P_D = 12 \text{ mmHg}, \sigma_{CG} = 0.5, \sigma_{TG} = 0.005, \) and two different tissue widths, \( L = 1 \text{ cm} \) (for example, human abdominal wall muscle) and \( L = 0.2 \text{ cm} \) (for example, rat abdominal wall muscle). The simulations were carried out for constant intraperitoneal hydrostatic pressure and glucose concentration, and therefore, after a short transient period (less than 20 minutes), a steady state of transport is reached.

A transient dehydration of tissue (represented in Figure 1 by the negative hydrostatic pressure) occurs during the initial minutes of fluid exchange, when water is suddenly pulled out of the tissue by high osmotic pressure at the peritoneal surface. However, the penetration of glucose into the tissue and its osmotic effect on blood results in replenishment of the interstitial water and an increase of hydrostatic pressure in the tissue to nonnegative values. This transient dehydration is more pronounced in the thin tissue layer (\( L = 0.2 \text{ cm} \)) and hardly visible for the thicker tissue layer (\( L = 1 \text{ cm} \)).

In the steady state, the hydrostatic pressure in the tissue continuously decreases from \( P = 12 \text{ mmHg} \) at the peritoneal surface, \( x = 0 \), to the zero level at the skin surface, \( x = L \). The tissue layer that is substantially altered because of contact with dialysis fluid is thin (about 1 mm from the peritoneal surface, Figure 1). In this layer, only the glucose concentration and hydrostatic pressure are higher than their respective physiologic values without dialysis, and a flow of water towards the peritoneal surface of the tissue is observed (Figure 1; the negative values of water flux in the tissue, \( j_V \), mean that the direction is toward the peritoneal surface at \( x = 0 \)).

Table I shows the values of ultrafiltration flux from the tissue to the peritoneal cavity, \( q_{U_P} \), obtained by computer simulations for three different values of intraperitoneal hydrostatic pressure. The values of the glucose reflection coefficient shown in Table I were selected to obtain \( P \) close to 0 at the skin surface. The calculated rates for \( q_{U_P} \) in the steady state were within the range 0.0014 – 0.0020 cm/min, and that result is equivalent to the total ultrafiltration rate, \( Q_{U} \), of 7 – 10 mL/min. Note that the values of \( \sigma_{TG} \) necessary to obtain the zero hydrostatic pressure at the skin surface are lower for lower values of \( P_D \). This situation reflects their role of preventing excessive fluid flow toward deeper layers of the tissue according to the hydrostatic pressure gradient. In a more realistic situation with fixed \( \sigma_{TG} \), some difference in the hydrostatic pressure at the skin surface would be expected for different values of \( P_D \). An interesting observation is that ultrafiltration from the thin tissue layer (\( L = 0.2 \text{ cm} \)) is more effective than from the thick tissue layer (\( L = 1 \text{ cm} \); Table I).

Discussion

Although the distributed model presented here of ultrafiltration to the peritoneal cavity induced by the high osmotic pressure of dialysis fluid is rather simple, we were able to demonstrate how transport parameter values influence the values of ultrafiltration flow and interstitial fluid hydrostatic pressure. Our previous simulations with \( \sigma_{CG} \) in the range 0.01 – 0.1 and \( \sigma_{TG} \) in the range 0.001 – 0.01 did not result in any satisfactory description of fluid flow and tissue hydration patterns. [Some of those results were presented in (9).]

Conclusions

The current results suggest that the capillary reflection coefficient for glucose should be expected to be at least 0.5, and that the tissue reflection coefficient should be small but higher than zero. The values of capillary reflection coefficients for small solutes were
FIGURE 1  Interstitial pressure, $P$ (upper panels); volumetric (fluid) flux, $j_V$ (middle panels); and interstitial glucose concentration, $C_G$ (lower panels), for tissue widths $L = 1$ cm (left panels) and $L = 0.2$ cm (right panels), for intraperitoneal pressure $P_D = 12$ mmHg and intraperitoneal glucose concentration $C_{GD} = 180 \times 10^{-3}$ mmol mL$^{-1}$. 
Distributed Modeling of Glucose-Induced Osmotic Flow

vigorously discussed by physiologists. In 1970, Pappenheimer formulated a hypothesis that these coefficients should have values between 0.5 and 1, despite the fact that the measured values at that time were not higher than 0.1 (10). High (0.3 – 0.5) values of reflection coefficients for small solutes were measured in cat skeletal and cardiac muscle and rabbit heart, but not in rat skeletal muscle (11–13). Therefore, although the data conflict, at least some physiologists support the idea of high values of the capillary reflection coefficients for small solutes. With regard to the reflection coefficients in the interstitium, no experimental data are available so far, and it may be difficult to directly measure a value as small as that predicted by our model.

References

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<th>Parameters</th>
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<td>$P_D$ (mmHg)</td>
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a The computer simulations using the values of $\sigma_{TG}$ shown here yielded a hydrostatic pressure close to $0$ at the external surface of the tissue.