Concomitant bidirectional transport during peritoneal dialysis can be explained by a structured interstitium

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Submitted 23 December 2014; accepted in final form 26 February 2016

Stachowska-Pietka J, Waniewski J, Flessner MF, Lindholm B. Concomitant bidirectional transport during peritoneal dialysis can be explained by a structured interstitium. Am J Physiol Heart Circ Physiol 310: H1501–H1511, 2016. First published April 3, 2016; doi:10.1152/ajpheart.00925.2014.—Clinical and animal studies suggest that peritoneal absorption of fluid and protein from dialysate to peritoneal tissue, and to blood and lymph circulation, occurs concomitantly with opposite flows of fluid and protein, i.e., from blood to dialysate. However, until now a theoretical explanation of this phenomenon has been lacking. A two-phase distributed model is proposed to explain the bidirectional, concomitant transport of fluid, albumin and glucose through the peritoneal transport system (PTS) during peritoneal dialysis. The interstitium of this tissue is described as an expandable two-phase structure with phase F (water-rich, colloid-poor region) and phase C (water-poor, colloid-rich region) with fluid and solute exchange between them. A low fraction of phase F is assumed in the intact tissue, which can be significantly increased under the influence of hydrostatic pressure and tissue hydration. The capillary wall is described using the three-pore model, and the conditions in the peritoneal cavity are assumed commencing 3 min after the infusion of glucose 3.86% dialysis fluid. Computer simulations demonstrate that peritoneal absorption of fluid into the tissue, which occurs via phase F at the rate of 1.8 ml/min, increases substantially the interstitial pressure and tissue hydration in both phases close to the peritoneal cavity, whereas the glucose-induced ultrafiltration from blood occurs via phase C at the rate of 15 ml/min. The proposed model delineate the phenomenon of concomitant bidirectional transport through PTS is based on a two-phase structure of the interstitium and provides results in agreement with clinical and experimental data.

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peritoneal hydrostatic pressure (12, 19). The hypertonicity of fresh dialysis fluid induces a high osmotic pressure gradient between the peritoneal cavity and surrounding tissues (44). The difference in concentrations of many solutes between the cavity and tissue creates a diffusive force for solute movement. Because of these simultaneously occurring forces, metabolic waste products and water enter the dialysate, and solutes in the fresh dialysis fluid including an osmotic agent (usually glucose) are absorbed to the body (Fig. 1).

Therefore, water transport between peritoneal cavity and the tissue occurs in two directions: hydrostatic-pressure driven fluid absorption from the peritoneal cavity and the osmotic-pressure driven ultrafiltration to the peritoneal cavity. Indirect evidence suggests that peritoneal absorption of fluid and protein (e.g., labeled albumin, dextran) from dialysis fluid to the tissue occurs concomitantly with ultrafiltration and convective leak of serum proteins from blood to dialysate (16, 18, 21, 28, 38, 47, 55). However, there is a lack of data on details of this bidirectional transport and especially how this transport can occur concomitantly in both directions during the peritoneal dwell. Until now no mathematical model has been developed that could provide a theoretical explanation of this bidirectional phenomenon. Such a model would be helpful, for example, to predict fluid absorption from peritoneal cavity, which may play a crucial role in the process of drug delivery, or to describe peritoneal transport and absorption of macromolecules (such as glucose polymers) from the peritoneal cavity during peritoneal dialysis or intraperitoneal chemotherapy (such as monoclonal antibodies or nanoparticles). The aim of this study was to test the hypothesis that a two-phase structure of the interstitium may explain such bidirectional transport of fluid and protein through PTS during dialysis.

The PTS is a complex, three-dimensional structure made up of peritoneum, the underlying tissue layer with interstitial matrix, blood, and lymph capillaries embedded within tissue. The anatomic peritoneum is composed of a single layer of mesothelial cells and four to five layers of connective tissue and is relatively avascular. The parietal tissue and the serosal side of the organs of the gastrointestinal tract (except for the solid organs such as the liver) are made up of muscle. The depth of tissue penetrated by solutes depends on many factors, such as solute size, hydrostatic and osmotic pressure gradients, type of dialysis, and transport characteristics of the individual patient. In the following, transport through the PTS, composed of the anatomical peritoneum and muscle tissue, will be further modeled, taking into account local physiology and structure of the system, assuming existence of two different phases within the interstitium (14, 51). The two-phase system contains a water-rich, colloid-poor region (fluid phase: phase F), where fluid
transport is driven by the hydrostatic pressure, and a colloid-rich, water-poor region (colloid phase: phase C; Fig. 2). The matrix of macromolecules of the interstitial “ground substance” (phase C) has an ordered structure mainly made up of collagen fibers, elastin, and glycosaminoglycans with hyaluronic acid. At physiological equilibrium, protein transport through an intact tissue not exposed to dialysis is channeled to the water-rich regions of the interstitium, because the colloid-rich regions are occupied by other macromolecules (23). This results in tortuous water pathways for protein transport between capillaries and lymphatic vessels. However, slow penetration of proteins into phase C also occurs. Therefore, one should expect that the viscous structure of phase C would result in significant retardation of solute transport, especially in the case of large molecules, whereas diffusivity of solutes in phase F should be similar to, or slightly less, than in water.

PHYSIOLOGICAL DATA ON FLUID AND MACROMOLECULES TRANSPORT THROUGH THE INTERSTITIUM

Experimental evidence for concomitant bidirectional fluid transport in peritoneal dialysis. Studies on the peritoneal transport of large molecules such as proteins show that macromolecules are transported mainly by convection (if fluid flow is sufficiently high), and therefore, their transport can serve as a surrogate marker of fluid transport. Transport of protein tracers from the peritoneal cavity, and native proteins in the opposite direction, may serve as indirect indicators of fluid transport.

Experiments on mice and rats with labeled albumin (RISA) show that, in parallel with the ultrafiltration flow to the peritoneal cavity, fluid and protein absorption from the peritoneal cavity occurs continuously throughout the dwell time, from the early minutes of the dialysis fluid exchange (28, 55). An exponential decay function of the RISA mass kinetic was found showing that fluid absorption from peritoneal cavity occurs irrespectively of ultrafiltration that brings water and solutes in the opposite direction (55). The initial rate of tracer disappearance from the peritoneal and fluid absorption is increased during the initial 30 min of peritoneal dwell, as predicted by the distributed model of fluid absorption (37).

Clearances from the peritoneal cavity, measured in clinical studies for dextrans with Einstein-Stokes radius from 30 to 90 Å, were similar, whereas the clearances of proteins from blood strongly depend on their molecular size (21). This suggests that, whereas protein transport from the peritoneal cavity is mostly convective, the diffusive or sieving properties of the interstitium play an important role in the transport of proteins in the opposite direction. No difference between clearances of albumin and IgG from plasma to dialysate for hypoosmolar and hypertonic solutions was observed (38) nor for other large proteins (18). Similarly, protein clearances for glucose 1.36 and 3.86% solutions do not differ (16, 18, 47). Protein clearances change with dwell time (47) and depend on the intraperitoneal pressure (17).

Experiments in rats showed only small difference in the tissue profiles of labeled IgG absorbed from the peritoneal cavity to the tissue at 20 min after infusion of isotonic or hypertonic solution (10). However, this difference disappeared after 200 min of peritoneal dwell (10). This indicates that initially, when ultrafiltration is high, it does not prevent fluid absorption from the peritoneal cavity and penetration of proteins into the tissue, but it slightly slows down their convective absorption driven by the hydrostatic pressure difference.

The rate of fluid absorption from the peritoneal cavity does not depend on fluid osmolality (38) but on intraperitoneal hydrostatic pressure and volume (17, 19). This indicates that water transport from...
the peritoneal cavity occurs concomitantly and independently of the amount of ultrafiltrated water.

**Two-phase structure of interstitium.** The interstitium contains a two-phase system (2, 6, 31) with two distinct parts: a colloid-rich and water-poor phase (phase C), and a water-rich and colloid-poor phase (phase F). The two phases are in equilibrium with each other (3, 9, 11, 13, 15, 31, 51). Although experimental observations and theoretical predictions tend to confirm the existence of at least two distinct phases within the interstitium, the precise designation of both phases seems to be somewhat arbitrary (3, 6). This is because the water-filled spaces are less apparent in the normal physiological state, due to paucity of free fluid in the interstitium (6, 22). The continuous water channels are visible, however, in edematous conditions when tissue hydration increases. The possible creation of new water channels with increased hydraulic conductivity of the interstitium was suggested also by Guyton et al. (14).

The direct experimental evidence for the two-phase concept is equivocal, although functional studies support this theory. Some authors questioned the results that were obtained in the early history of electron microscopy (15). However, later measurements by photon fluorescence microscopy showing fast protein transport in the water-rich regions of interstitium and slow in the colloid-rich regions seem to confirm the two-phase hypothesis (1, 7). The microscopy studies by Barber and Nearing (4) showed high degree of heterogeneity within the interstitium with some regions being almost devoid of plasma proteins, whereas channels of interstitial fluid with a protein concentration of about two-thirds that of plasma were observed in other regions. The experimental evidence for faster transport of large molecules from blood to lymph suggests that interstitium acts analogously to a gel chromatography column (5, 49, 50), and movement of injected dyes in various tissue has been reported (23, 24). The dyes appeared initially in preferential channels in the interstitium indicating that the dyes are transported “around” the gel phase and not through it (23). There are similar results in studies on tissue uptake of radiolabeled tracers injected intravenously (25, 26). Recently, there has been an increased interest in the quantification of transport through the structured interstitium and its role in anticancer drug delivery. New experimental methods may provide more accurate measurements on various transport parameters in each phase of interstitium (1, 20, 27, 39).

**MODEL FORMULATION**

In the following section, a mathematical model of the two-phase structured interstitium is formulated. The description of the PTS, its structure and flows, is based on classical, thermodynamic forces and experimental evidence on the peritoneal structure and major barriers for the peritoneal transport. For a more detailed mathematical description of the major concepts presented in this section and mass balance equations of the whole system, see the APPENDIX.

**Two-phase structure of the muscle tissue and the anatomical peritoneum.** Based on experimental studies, it was assumed that interstitium is composed of two different phases. In this case, the total interstitial fluid void volume ratio, \( \theta \), can be calculated as the sum of fluid void volume ratios in each of two phases:

\[
\theta = \theta_1 + \theta_2
\]

where \( \theta_1 \) and \( \theta_2 \) are the corresponding interstitial fluid void volume ratios in phase F and C, respectively. In general, hydration in each phase may change due to the local fluid movements. Let us denote by \( x_i^0 \), the initial fraction of the overall interstitial fluid void volume ratio that corresponds to phase \( i \), where \( i = 1 \) denotes phase F, \( i = 2 \) denotes phase C, subscript 0 stands for the initial value (at \( t = 0 \)), and \( x_1^0 + x_2^0 = 1 \). The initial values of the variables (at \( t = 0 \)) were selected to describe the normal physiological state. Experimental data suggest that in such a state a “paucity of free fluid is thought to exist within the interstitium” and therefore the fluid channels of phase F are hardly seen (6). Therefore, for the purpose of computer simulations, the existence of an initial, low fraction of phase F (\( x_1^0 = 5% \)) was assumed with the possibility for further increase (channels in Fig. 2).

The structure of the anatomical peritoneum differs from that of the abdominal wall muscle. In the model, the blood vessels and lymphatics were assumed to be absent in the anatomical peritoneum, which was assumed to be mostly composed of the two-phase interstitium and simulated as a layer of 150-μm wide within the PTS and present at the peritoneal surface of the muscle, according to the data for uremic patients; see Fig. 3 (8, 53). Note that since we consider ratio of interstitial fluid void volume per tissue unit (not interstitium), the interstitial fluid void volume ratio of the peritoneum in general would differ from that of abdominal wall partially due to the number of cells that occupy muscle space. Let us denote the part of the overall interstitial fluid void volume ratio that corresponds to the anatomical peritoneum by \( \theta^{\text{PERL}} \). The existence of the peritoneum implied that the initial interstitial fluid void volume ratio differs within the tissue, changing from \( \theta^{\text{PERL}} \) in the anatomical peritoneum to \( \theta_0 \) in the abdominal wall muscle, with some transitional region. The proper mathematical description of this transition requires application of a switching function as presented in detail in the APPENDIX.

Infusion of fluid into the peritoneal cavity induces water inflow from the peritoneal cavity to the adjacent tissue and results in the increase of overall interstitial fluid void volume ratio to the value of \( \theta(t, x) \) at time \( t \) and distance from the peritoneal cavity, \( x \) (37). However, the participation of each phase in this increment may be different. Although the expansion of phase F and free fluid channels has not been directly demonstrated, Guyton et. al (14) pointed out the very high hydraulic conductivity of edematous subsalts and suggested that increased hydration may create continuous water-filled space. Let us denote by \( V_{\text{inc}} \) the fractional increase of the interstitial fluid void volume in phase \( i \) due to the increase of the overall fluid void volume \( \theta \) over its initial value, \( \theta_0 \), and then, \( V_{\text{inc}} + V_{\text{inc}}^2 = 1 \). Let us assume that the increment of the interstitial fluid would be preferably “pumped” into the fluid phase and therefore \( V_{\text{inc}}^1 > V_{\text{inc}}^2 \). In this case, the interstitial fluid void volume ratio can be calculated in each phase and at each time and position in the tissue, \( (t, x) \), as the sum of initial fluid void volume, \( \theta_0^i \), and the increment of tissue hydration in this phase at time \( t \) as:

\[
\theta^i = \theta_0^i + V_{\text{inc}}^i \cdot (\theta - \theta_0^i)
\]

where \( \theta \) denotes the total interstitial fluid void volume ratio in the tissue at time \( t \) and distance \( x \), which corresponds to the given value of interstitial hydrostatic pressure in phase \( i \), \( P^i \).

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**Fig. 3.** Schematic structure of fluid fluxes in the model between compartments, where \( j_{v}^i(t,0) \) and \( j_{v}^i(t,0) \) denotes fluid flux across the peritoneal surface from phase F and phase C, respectively; \( q_{\text{inc}}^1 \), \( q_{\text{inc}}^2 \) denote fluid flux across the capillary wall to phase F and phase C; and \( q_{\text{inc}}^1 \) and \( q_{\text{inc}}^2 \) denote lymphatic absorption from phase F and C, respectively. Solute fluxes have a similar scheme.
Finally, the share of interstitial fluid volume ratio in phase \( i \) in the overall interstitial fluid void volume ratio, \( \chi'(i) \), may change during the dwell time from its initial value, \( \chi_0(i) \), and this time evolution can be calculated as:

\[
\chi'(i) = \frac{\theta'(i)}{\theta(i)^2} (3)
\]

Fluid transport through the tissue (anatomical peritoneum and muscle). In general, the equations for the fluid transport through the structured interstitium are similar to those proposed and applied before based on distributed modeling applied to peritoneal dialysis (35, 37). Although the structure of the equations is kept, the existence of two-phases implies additional decomposition of the equations describing transport through each phase and additional equations for the exchange between phases. The schematic structure of fluid fluxes in the model between compartments is presented in Fig. 3. The changes in the fluid void volume in each phase \( i \) are due to the fluid flux through this phase increased by the net fluid inflow to the phase, which can be either from internal sources/sinks such as blood and lymph or from the interphase exchange.

The fluid flux through the tissue can be described by the extended Darcy law, according to which the fluid flux is driven by hydrostatic, colloid osmotic and oncotic pressure gradients (46). Hence,

\[
\dot{j}_V = - \theta'(i) \left( \frac{\partial P^i}{\partial x} - \sigma_T^i RT \frac{\partial C^i}{\partial x} - \sigma_{Alb}^i \frac{\partial \Pi^i}{\partial x} \right) (4)
\]

where \( \dot{j}_V \) denotes fluid flux through the phase \( i \), and the phase index that can be either 1 or 2; \( K^i \) is the hydraulic conductivity in phase \( i \); \( \theta'(i) \) is the effective hydraulic conductivity of phase \( i \); \( P^i, C^i, \) and \( \Pi^i \) are, respectively, the interstitial pressure, glucose concentration, and oncotic pressure in phase \( i \); \( RT \) is constant; and \( \sigma_T^i \) and \( \sigma_{Alb}^i \) are the tissue reflection coefficient to glucose and proteins in phase \( i \), respectively. In the model albumin is taken as a representative protein, and the time evolution of the interstitial oncotic pressure is considered based on the changes in the albumin concentration; see the APPENDIX for more details. It was assumed that the tissue reflection coefficient in phase \( F \) is equal to \( \sigma_{T,G}^\text{cap} \) for albumin and glucose, whereas positive values of tissue reflection coefficients in phase \( C \) were considered.

In each phase \( i \), net fluid inflow through the blood capillary, \( q_{\text{cap},i} \), is decreased by the local lymphatic absorption from phase \( i \), \( q_L \). It is assumed that fluid exchange through the capillary wall can be calculated according to the Starling law and the three-pore model of the capillary wall (30, 48). Therefore, assuming that the osmotic pressure difference across capillary wall is exerted by glucose and albumin, the net fluid inflow into the tissue from the internal source/sink is equal to

\[
q_V = q_{\text{cap},i} - q_L (5)
\]

with the net fluid inflow through the blood capillary being the sum of the flows through each pore type (ultrasmall, small or large pore) given by the following equation:

\[
q_{\text{cap},i} = q_{\text{cap},i}^\text{P} - L_{\text{cap},i}^\text{P} (P_B - P^i) - L_{\text{cap},i}^\text{G} (C_L - C_G^i) - L_{\text{cap},i}^\text{Alb} (C_L - C_A^i) (6)
\]

where \( P_B, \Pi_L, \) and \( C_L \) are the hydrostatic and oncotic blood pressure and glucose concentration in blood, respectively; \( L_{\text{cap},i}^\text{P} \) is the hydraulic conductance of the pore in the capillary wall in phase \( i \); \( \sigma_{\text{cap},i}^\text{G} \) and \( \sigma_{\text{cap},i}^\text{Alb} \) are the capillary wall reflection coefficients of glucose and albumin, respectively; and the subscript “pore” stands for either ultrasmall, small, or large pore type (see e.g., Ref. 30 for more details on pore modeling of transport across the capillary wall). Experimental data show that lymphatic absorption may increase in response to increased interstitial hydrostatic pressure and tissue hydrodynamics (37). Therefore, \( q_L \) was modeled similarly to our previous approaches but with the additional split to each phase and by taking into account the lack of lymphatics in the anatomical peritoneum; see the APPENDIX for more details.

In general, fluid exchange between two phases is driven by the interstitial hydrostatic pressure and solute concentration difference between phases. Therefore, the net fluid flow from phase \( F \) to phase \( C \) can be calculated as follows:

\[
q_V^{1-2} = L_{\text{cap},i}^\text{2} (P_1^i - P_2^i - \sigma_{G}^{1-2} \cdot RT \cdot (C_G^1 - C_G^2) - \sigma_{Alb}^{1-2} \cdot (\Pi_1 - \Pi_2)) (7)
\]

where \( L_{\text{cap},i}^{1-2} \) is the interphase hydraulic conductances for fluid, \( \sigma_{G}^{1-2} \) and \( \sigma_{Alb}^{1-2} \) are, respectively, the interphase reflection coefficients for glucose and albumin, which were assumed to be the same as in phase \( C \). Typically, the peritoneum has higher density of the interstitium that abdominal wall muscle. Therefore, in the model higher interphase hydraulic conductance in the peritoneum layer was considered than in the muscle; see the APPENDIX for more details on the mathematical formulation of the space dependence of the \( L_{\text{cap},i}^{1-2} \).

Solute transport through the tissue (anatomical peritoneum and muscle tissue). The amount of solute in each phase may change due to the solute flux across the phase, the net inflow of solutes from the internal source/sink such as blood or lymph, and the exchange between the interstitial phases. The solute flux across phase \( i \), \( j_s \), can be diffusive (caused by the solute concentration gradient) and convective due to the fluid flux through the tissue. It comes from the general thermodynamic equation that solute flux across phase \( i \) can be calculated as:

\[
j_s = - \theta_s D_s^i \frac{\partial C_s^i}{\partial X} + (1 - \sigma_{G}^i) \cdot C_s^i \cdot j_V (8)
\]

where \( \theta_s D_s^i \) is the effective diffusivity of solute \( S \) in phase \( i \), \( D_s^i \) is the tissue diffusivity in phase \( i \). It was assumed that glucose and albumin void volume in each phase \( i, \theta_G^i \) and \( \theta_{Alb}^i \) were equal to the interstitial fluid void volume in each phase \( i \), i.e., \( \theta_G^i = \theta_{Alb}^i = \theta_s^i \).

The net solute inflow into the tissue from the internal sources/sinks (per unit tissue volume), \( q_s \), is due to combined diffusive and convective solute inflow through the capillary wall into the tissue in each phase decreased by the amount of solute absorbed by lymphatic absorption from this phase and is given by the following equation:

\[
q_s^i = (p_s(a' - C_S^i)) \sum_{\text{pore} = \text{SP,LP}} (1 - \sigma_{G}^i \cdot C_{S}^i \cdot j_V^i - \sigma_{Alb}^i \cdot (C_{S}^i - C_{Alb}^i) \cdot \dot{j}_V (9)
\]

where \( \theta_s D_s^i \) is the solute diffusive permeability of the capillary wall in phase \( i \) (per unit tissue volume), \( C_{S}^i \) and \( C_{S}^i \) are, respectively, solute blood and phase \( i \) interstitial concentration of solute \( S \), and \( f \) is the solute specific weighting factor, and “pore” stands for pore type, which can be either small (SP) or large pore (LP).

The solute flow from phase \( F \) to phase \( C \) (per unit tissue volume) can be calculated according to classical thermodynamic approach as (40):

\[
q_s^{1-2} = p_s (C_S^1 - C_S^2) + (1 - \sigma_{G}^{1-2}) q_V^{1-2} (1 - f_{T}^{1-2} - C_S^2) (10)
\]

where \( p_s \) is the interphase diffusive permeability for solute transport (per unit tissue volume) and \( f_{T}^{1-2} \) is the interphase weighting factor for solute concentration. Finally, in the description of interphase diffusive permeability, the differences in the density of the interstitium between the anatomical peritoneum and muscle layer should be taken into account in a similar way as for \( L_{\text{cap},i}^{1-2} \), see the APPENDIX for more details.

Exchange across the capillary wall. In this study, the three-pore model of the capillary wall was applied to describe microvascular exchange with modifications for two interstitial phases and the distribution of the capillaries and lymphatics in the tissue, since no blood
supply was assumed in the anatomical peritoneum. In particular, it was assumed that properties of the capillary wall are the same for both phases and that capillaries are distributed uniformly in the muscle layer. Therefore, the capillary wall reflection coefficient, \( \sigma_i^{(c)} \), although it may vary among solutes, remains the same in both phases for each particular solute. Note that since the effective surface area of the capillary bed per phase is different between phases, the corresponding hydraulic conductance, \( L_{ap}i \), and solute permeability, \( (p_{sa}i) \), should be calculated for each phase \( i \) separately, with the respect to the differences in the interstitial fluid volume distribution between phases and the lack of the capillaries in the peritoneum; see the APPENDIX for more details.

**RESULTS**

Numerical simulations with initial and boundary conditions, as defined in the APPENDIX, were performed for the transport of water, glucose as an osmotic agent, and albumin representing proteins. Therefore, the time and space evolutions of six variables, which describe interstitial pressure and solute concentration in both phases, were considered. Equations 1–28 were solved numerically using Matlab software with pdepe solver in the human peritoneal tissue that was composed of an anatomical peritoneum and abdominal wall muscle layers for 60 min after fluid infusion into the peritoneal cavity (8, 53).

Table 1 shows values of parameters, assumed based on previous studies. The parameters that correspond to the three-pore structure of the capillary wall were calculated according to the general theory, for each pore type and each solute separately for a given set of parameters, which was assumed to be the same in both phases, see Table 1 and Ref. 30. Due to the lack of quantitative data on the parameters related to the two-phase structure of the interstitium, the assumed values were chosen in such a way to reflect qualitative experimental data and to remain in agreement with the quantitative data from the clinical studies in peritoneal dialysis; see Table 2. Please note that whereas the parameters related to the two-phase structure were assumed based on qualitative information from experimental studies, the parameters related to its transport properties were selected in a series of computer simulations to provide net characteristics of fluid, glucose, and serum albumin measured in clinical studies (Table 2). As one would expect, the obtained values of transport parameters in phase \( \text{C} \), such as tissue diffusivity and hydraulic conductivity, were found to be substantially lower than in phase \( \text{F} \).

Infusion of dialysis fluid into the peritoneal cavity increased intraperitoneal hydrostatic pressure and, in consequence, induced fluid absorption from the peritoneal cavity into the PTS. Concomitantly, a high concentration of glucose resulted in ultrafiltration flow into the peritoneal cavity. Computer simulations demonstrated that (in the quasi-steady state) the peritoneal fluid absorption into the PTS occurred via phase \( \text{F} \) at the rate 1.77 ml/min (at 1 h after fluid infusion; Fig. 4). The concomitant glucose-induced ultrafiltration, from blood via phase \( \text{C} \) to the peritoneal cavity, was at the rate of 15.16 ml/min; see Fig. 4.

The changes in the interstitial hydrostatic pressure and tissue hydration in both phases are presented in Fig. 5. The inflow of water into the PTS across the capillary wall (mostly in phase \( \text{C} \)) and from the peritoneal cavity (mostly in phase \( \text{F} \)) increased substantially the interstitial hydrostatic pressure and tissue hydration (fluid void volume) in both interstitial phases within the layer of about 0.3–0.4 cm in width (Fig. 5).

Glucose diffused from the peritoneal cavity into both phases of interstitium, where it was quickly absorbed to blood. Therefore, local glucose concentration in each phase gradually decreased to equilibrate with plasma within 0.2-cm distance from the peritoneal surface, remaining unchanged in the deeper part of the tissue (Fig. 6). The similarities between glucose concentration profiles in both phases are the consequence of the

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Table 1. The transport parameters assumed for computer simulations of peritoneal dialysis based on the published studies

<table>
<thead>
<tr>
<th>Parameter, unit</th>
<th>Parameter Description</th>
<th>Value</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>( L, \text{cm} )</td>
<td>Tissue width</td>
<td>1</td>
<td>(35, 37)</td>
</tr>
<tr>
<td>( \Delta_{\text{PERL}, \text{cm}} )</td>
<td>Width of the peritoneum</td>
<td>0.015</td>
<td>(8, 53)</td>
</tr>
<tr>
<td>( P_0, \text{mmHg} )</td>
<td>Initial interstitial hydrostatic pressure</td>
<td>0</td>
<td>(35, 37)</td>
</tr>
<tr>
<td>( P_D, \text{mmHg} )</td>
<td>Intraperitoneal hydrostatic pressure</td>
<td>7</td>
<td>(35, 37)</td>
</tr>
<tr>
<td>( P_H, \text{mmHg} )</td>
<td>Blood hydrostatic pressure</td>
<td>16</td>
<td>(42)</td>
</tr>
<tr>
<td>( \Pi_0, \text{mmHg} )</td>
<td>Blood oncotic pressure</td>
<td>22.88</td>
<td>(42)</td>
</tr>
<tr>
<td>( \Pi_G, \text{mmHg} )</td>
<td>Initial interstitial oncotic pressure in phase ( \text{F} ) and ( \text{C} ), respectively</td>
<td>8</td>
<td>(29)</td>
</tr>
<tr>
<td>( C_{B,G, \text{mmol/ml}} )</td>
<td>Glucose concentration in plasma</td>
<td>0.006</td>
<td>(43)</td>
</tr>
<tr>
<td>( C_{D,G, \text{mmol/ml}} )</td>
<td>Glucose concentration in dialysate</td>
<td>0.18</td>
<td>(43)</td>
</tr>
<tr>
<td>( C_{B,\text{Ab}, \text{mmol/ml}} )</td>
<td>Albumin concentration in plasma</td>
<td>0.049</td>
<td>*</td>
</tr>
<tr>
<td>( C_{D,\text{Ab}, \text{mmol/ml}} )</td>
<td>Albumin concentration in dialysate</td>
<td>0.00015</td>
<td>*</td>
</tr>
<tr>
<td>( \rho_{SP}, \text{Å} )</td>
<td>Small pore radius</td>
<td>39</td>
<td>(48)</td>
</tr>
<tr>
<td>( \rho_{LP}, \text{Å} )</td>
<td>Large pore radius</td>
<td>300</td>
<td>(48)</td>
</tr>
<tr>
<td>( \Sigma a_{\Delta x, \text{cm/ml}} )</td>
<td>Capillary surface area over diffusion distance</td>
<td>205</td>
<td>(48)</td>
</tr>
<tr>
<td>( \Sigma a_{\Delta x, \text{cm/ml}} )</td>
<td>Fractional share of ultrasmall pores in the overall hydraulic conductance</td>
<td>0.035</td>
<td>(48)</td>
</tr>
<tr>
<td>( \theta_{\min} )</td>
<td>Minimal value of interstitial fluid void volume ratio</td>
<td>0.177</td>
<td>(46, 54)</td>
</tr>
<tr>
<td>( \theta_{\max} )</td>
<td>Maximal value of interstitial fluid void volume ratio</td>
<td>0.36</td>
<td>(46, 54)</td>
</tr>
<tr>
<td>( \theta_0 )</td>
<td>Value of interstitial fluid void volume ratio for ( P = 0 )</td>
<td>0.18</td>
<td>(46, 54)</td>
</tr>
<tr>
<td>( \beta )</td>
<td>Sensitivity of interstitial fluid volume ratio to increase in ( P )</td>
<td>2.019</td>
<td>(46, 54)</td>
</tr>
<tr>
<td>( A_0, \text{cm}^2 )</td>
<td>Effective peritoneal surface area of the contact with dialysate</td>
<td>6000</td>
<td>(35)</td>
</tr>
</tbody>
</table>

*Based on typical, clinical data from Karolinska Institutet, Stockholm, Sweden.

AJP-Heart Circ Physiol • doi:10.1152/ajpheart.00925.2014 • www.ajpheart.org
assumptions on the properties of each phase and the fast transport between phases. Glucose can easily penetrate both phases and flows between them, and therefore, no substantial difference for most neutral small solutes is expected.

The albumin concentration in the tissue decreased close to the peritoneal cavity due to dilution by the inflow of albumin-free water from the peritoneal cavity (in phase F) and blood (in phase C) and due to albumin removal to the peritoneal cavity in phase C, Fig. 7. The clearance of serum albumin obtained from computer simulations was equal to 0.2 ml/min and was caused mostly by albumin transport to the peritoneal cavity from phase C.

Special attention should be paid to the six parameters, which were assumed (based on the literature) but were not adjusted and not used and tested in previous models; those are parameters of the peritoneal layer such as \( \Theta^{\text{PERL}} \), \( \chi_{0}^{\text{PERL}} \), and of the two-phase structure of the interstitium: \( n \), \( a \), \( \chi_{0} \), \( \Theta^{\text{inc}} \). The thickness of the peritoneal layer mainly affects the peritoneal absorption. The growing thickness of the layer from 100 through 150 to 200 \( \mu \)m (as observed for healthy subjects, uremic patients, and patients on peritoneal dialysis) would result in increase of peritoneal absorption from 1.5 through 1.8 to 2.0 ml/min and a slight decrease of ultrafiltration from 14.9 to 15.3 ml/min. The increase of the remaining five parameters by 10% has only small effect on the output parameters such as peritoneal absorption, ultrafiltration and albumin clearance. The rate of peritoneal absorption from the peritoneal cavity can be influenced mainly by \( \Theta^{\text{PERL}} \) with decrease of the peritoneal absorption by 5%, whereas the modification of \( \Theta^{\text{inc}} \) and \( a \) would result in the increase of absorption by 4 and 2%, respectively. The negative impact on net ultrafiltration and albumin clearance relates to \( \Theta^{\text{inc}} \) (4%), whereas \( \Theta^{\text{PERL}} \) has positive effect with 3% increase. In addition, albumin clearance is mainly sensitive to the changes in \( \Theta^{\text{inc}} \) and \( \Theta^{\text{PERL}} \) resulting in its decrease by 4% and increase by 3%, respectively. To give some insight into the model prediction under different clinical conditions, the impact on the peritoneal absorption rate, ultrafiltration, and albumin clearance caused by the changes in the intraperitoneal pressure, glucose concentration, and the width of the anatomical peritoneum is calculated and presented in Fig. 8.

**DISCUSSION**

The one-phase models allow for description of either ultrafiltration flow and small solute transport or the absorption of

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**Table 2. The transport parameters that describe two-phase structure: assumed or adjusted based on computer simulations, qualitative experimental data on the two-phase structure, and quantitative data on fluid and solute flows from clinical studies**

<table>
<thead>
<tr>
<th>Parameter, unit</th>
<th>Parameter Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameters assumed based on qualitative data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \Theta^{\text{PERL}} )</td>
<td>Interstitial fluid void volume of the anatomic peritoneum</td>
<td>0.6</td>
</tr>
<tr>
<td>( n )</td>
<td>Switching ratio of the switching function ( \chi^{\text{PERL}} )</td>
<td>10</td>
</tr>
<tr>
<td>( a )</td>
<td>Parameter that describes the relative increase of transport parameters in the anatomic peritoneum over those in the muscle in the two-phase model</td>
<td>2</td>
</tr>
<tr>
<td>( \chi_{0}^{\text{PERL}} )</td>
<td>Initial fraction of the overall interstitial fluid void volume that corresponds to phase F</td>
<td>0.05</td>
</tr>
<tr>
<td>( \Theta^{\text{inc}} )</td>
<td>Fractional increase of interstitial fluid void volume in phase F due to the increase of the overall fluid void volume</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Parameters adjusted

<table>
<thead>
<tr>
<th>Parameter, unit</th>
<th>Parameter Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( K^{1} ), cm(^2)-min(^{-1})-mmHg(^{-1} )</td>
<td>Hydraulic conductivity of the tissue in phase F</td>
<td>1.03 ( \times ) ( 10^{-4} )</td>
</tr>
<tr>
<td>( K^{2} ), cm(^2)-min(^{-1})-mmHg(^{-1} )</td>
<td>Hydraulic conductivity of the tissue in phase C</td>
<td>0.28 ( \times ) ( 10^{-4} )</td>
</tr>
<tr>
<td>( \sigma_{\text{Alb}}^{1}, \sigma_{\text{Alb}}^{2} )</td>
<td>Albumin and glucose tissue reflection coefficient in phase F</td>
<td>0</td>
</tr>
<tr>
<td>( \sigma_{\text{Alb}}^{1}, \sigma_{\text{Alb}}^{2} )</td>
<td>Albumin reflection coefficient in the tissue in phase C and between phases</td>
<td>0.04</td>
</tr>
<tr>
<td>( \sigma_{\text{Al}}^{1}, \sigma_{\text{Al}}^{2} )</td>
<td>Glucose reflection coefficient in the tissue in phase C and between phases</td>
<td>0.009</td>
</tr>
<tr>
<td>( D_{\text{G}}^{1} ), cm/min</td>
<td>Glucose diffusivity in phase F</td>
<td>5.26 ( \times ) ( 10^{-4} )</td>
</tr>
<tr>
<td>( D_{\text{G}}^{2} ), cm(^2)-min(^{-1} )</td>
<td>Glucose diffusivity in phase C</td>
<td>2.63 ( \times ) ( 10^{-4} )</td>
</tr>
<tr>
<td>( D_{\text{Alb}}^{1} ), cm(^2)-min(^{-1} )</td>
<td>Albumin diffusivity in phase F</td>
<td>3.05 ( \times ) ( 10^{-5} )</td>
</tr>
<tr>
<td>( D_{\text{Alb}}^{2} ), cm(^2)-min(^{-1} )</td>
<td>Albumin diffusivity in phase C</td>
<td>0.76 ( \times ) ( 10^{-5} )</td>
</tr>
<tr>
<td>( L_{\text{pscl}}^{\text{PERL}} ), 1-min(^{-1})-mmHg(^{-1} )</td>
<td>Interphase hydraulic conductance for fluid in the muscle layer</td>
<td>7.4 ( \times ) ( 10^{-3} )</td>
</tr>
<tr>
<td>( P_{\text{pscl}}^{\text{PERL}} ), 1/min</td>
<td>Interphase diffusive permeability for glucose transport in the muscle layer</td>
<td>6.7 ( \times ) ( 10^{-1} )</td>
</tr>
<tr>
<td>( P_{\text{Alb}}^{\text{pscl}} ), 1/min</td>
<td>Interphase diffusive permeability for albumin transport in the muscle layer</td>
<td>8.9 ( \times ) ( 10^{-6} )</td>
</tr>
</tbody>
</table>
fluid and macromolecules from the peritoneal cavity. However, to model bidirectional concomitant flows one has to introduce additional structure. A spatially distributed model with a structured interstitium was proposed and tested, incorporating description of fluid and solute transport from the one-phase models into the two-phase structure. The model assumes that the bidirectional transport function of PTS is due to the existence of two phases of the interstitium, water rich and colloid rich, respectively. The model incorporates current knowledge on this putative two-phase structure and explains the existence of concomitant bidirectional transport of fluid and solutes after perturbation induced by inflow of dialysis fluid into the peritoneal cavity, resulting in modification in the structure and physiological parameters of the PTS. Some details and numerical values of the parameters were assumed to obtain agreement between the results of numerical simulations and available clinical data (Tables 1 and 2). This approach yielded a model that could reproduce to some extent the transperitoneal flows and clinical parameters previously measured in experimental and clinical studies. Numerical simulations showed that the steady state in the PTS tissue (for high ultrafiltration rate to the peritoneal cavity as observed at the beginning of a dwell with glucose 3.86% solution) cannot be obtained in a reasonable dwell time with constant glucose concentration in the peritoneal cavity. Such conditions can be of course only hypothetical, because the real dialysate glucose concentration in the peritoneal cavity quickly decreases and ultrafiltration drops. The permanently high ultrafiltration flow results in slow but persistent depletion of tissue albumin, and the zone with very low albumin concentration slowly penetrates the whole tissue (as seen in the computer simulations for dwell times longer than 1 h; data not shown). Therefore, the results are presented for only 1-h dwell time, when the fast transient changes after the perturbation of the physiological equilibrium die out and the flow rates are relatively stable. After that time, the system slowly drifts into states far from realistic conditions during dialysis.

The two-phase model indicated a different role of each phase: transport of water and solutes from the peritoneal cavity occurs mostly through phase F, whereas phase C is mainly...
utilized for the transport in the opposite direction. Fluid absorption, which occurs in phase $F$, calculated from computer simulation, was found to be 1.77 ml/min, which is within the range of the values observed clinically (0.9 – 2.3 ml/min range; Ref. 41). The rate of ultrafiltration (15.16 ml/min), which passes through phase $C$, remained in agreement with clinical data, where values of initial ultrafiltration within the range from 14.8 to 17.5 ml/min were reported (33, 34, 45). The computer simulations predicted that transport of albumin occurs mostly through phase $C$, and its clearance to the peritoneal cavity was found to be equal to 0.2 ml/min. Similar values were reported for the initial 15 min of peritoneal dialysis with different concentration of glucose in dialysate (47). The process of washing out albumin from the layers close to the peritoneal cavity (within the distance of 0.2 – 0.3 cm from peritoneal cavity), obtained in computer simulations, was also observed experimentally (32); investigators found a decrease in oncotic pressure in the tissue during dialysis together with a stable value of oncotic pressure in the subcutaneous layer.

Unfortunately, there are presently no available data to verify the role, structure, or function of the assumed two phases within the interstitium during the peritoneal dwell. There is also no information available that can validate transport parameters across and between both phases. The transient dehydration (observed as negative interstitial hydrostatic pressure) in phase $C$ after the start of dialysis does not seem to reflect the real dialysis situation but is the result of sudden change in osmotic pressure at the surface of the tissue; modeling of fluid infusion as a slow process would cause disappearance of this effect. Overall, the results provided by the model appear to be promising and may suggest possible directions and extensions of new experiments that are needed to verify the model. The so far successful validation of the model shows that it provides a physiologically based description of the PTS anatomy and its changes during dialysis, and, in the future, it might be possible to take into account also pathological changes that occur in the PTS during long-term dialysis. Moreover, further extension of the model, such as simulation of consecutive dialysis ex-

![Fig. 7. Albumin (Alb) concentration profiles in phase F (A) and phase C (B) of interstitium at different dwell times as a function of distance from the peritoneal cavity ($x$ = 0 corresponds to the peritoneal surface). The dashed lines correspond to the profiles for the consecutive dwell time steps starting from the bold dashed line with the time interval between profiles of 5 min, the arrows depict the order of profiles in time, and the solid line corresponds to the final profile obtained 60 min after infusion.](image)

![Fig. 8. The impact of the changes in the model parameters on the peritoneal absorption rate, ultrafiltration, and albumin clearance measured as a ratio of the new model to the basal model (denoted as model 0). The changes in the intraperitoneal hydrostatic pressure, solute concentration, and anatomical peritoneum width were considered as presented in the legend (the change in percent was specified in the bracelets), with the rest of the parameters remaining unchanged, as in Tables 1 and 2. For the simulations, the glucose concentrations in dialysate were assumed equal to 0.105 and 0.065 mmol/ml for glucose 2.27% and glucose 1.36% dialysis fluids, respectively (16).](image)
changes together with the kinetics of fluid and solutes in dialysate, could provide more information and allow to simulate the whole spectrum of the changes that occur during peritoneal dialysis.

Conclusions. The proposed distributed model with structured interstitium was able to describe a process of bidirectional water and protein transport through the peritoneum, yielding data that are in good agreement with data on fluid flows and solute clearances derived from clinical studies. The model explains this phenomenon of a bidirectional, concomitant flow of fluid and solutes by demonstrating that whereas the transport of water and solutes from the peritoneal cavity occurs mostly in one phase, phase F, of the interstitium, the transport in the opposite direction, i.e., to the peritoneal cavity, occurs across another phase, phase C.

The model predicts that fluid absorption stabilizes quickly after fluid infusion, in contrast to the longer lasting ultrafiltration flow induced by the high glucose concentration in the dialysis fluid. It also suggests that glucose concentration in the tissue stabilizes much quicker than interstitial pressure, tissue hydration, or concentration of proteins, which need longer time to reach steady state. Computer simulations of the two-phase model provide also information on the process of washing out of albumin close to the peritoneal surface, and therefore decreasing of oncotic pressure, after initiation of peritoneal dialysis.

APPENDIX

The introduction of two-phase structure of the interstitium, as well as the anatomic peritoneum without blood and lymphatic supply, requires additional mathematical modeling as presented below.

Note that in the case of no peritoneum, the initial interstitial void volume ratio in each phase would be calculated as \( \theta_0 = \chi_0 \theta_0 \), where \( \chi_0 \) is the initial fraction of the overall interstitial fluid void volume ratio that corresponds to phase i and \( \theta_0 \) is the rate of interstitial fluid void volume of the abdominal wall. However, in general, the rate of interstitial fluid void volume per tissue unit, \( \theta_0 \), differs between peritoneum and muscle layer, changing from \( g_{\text{PERL}} \) in the anatomic peritoneum to \( \theta_0 \) in the abdominal wall muscle with some transitory region. This can be formulated mathematically as follows:

\[
\theta_0(x) = \chi_0 \left[ \theta_{\text{PERL}}(x) - \theta_0 \theta_{\text{PERL}}(x) \right]
\]

where, function \( g_{\text{PERL}} \) is a switching function that changes from 0, at the peritoneal surface (\( x = 0 \)), to 1 in the abdominal wall muscle layer, to allow for smooth transition from the anatomic peritoneum to the muscle layer. The switching function \( g_{\text{PERL}} \) is a function of the distance from the peritoneal surface, \( x \), defined as follows:

\[
g_{\text{PERL}}(x) = \frac{x^n}{(x_{\text{PERL}})^n + x^n}
\]

where \( n \) is a constant parameter.

The changes in the tissue hydration in each phase as well as the solute transport within and between phases, induce changes in the oncotic pressure. Let us assume, that changes in the interstitial oncotic pressure in each phase follow changes in the albumin concentration in such a way that (36):

\[
\Pi' = \frac{\Pi_0}{C_{0,Alb}} C_{Alb}'
\]

where \( \Pi_0 \) is the initial tissue oncotic pressure in phase i, \( C_{0,Alb} \) is the initial tissue concentration of albumin in phase i, and \( C_{Alb}' \) is the actual tissue concentration of albumin in phase i. Therefore, the oncotic gradient in each phase can be calculated from the above equation as:

\[
\frac{\partial \Pi'}{\partial x} = \frac{\Pi_0}{C_{0,Alb}} \frac{\partial C_{Alb}'}{\partial x}
\]

Experimental studies suggest that lymphatic absorption may increase in response to increased interstitial hydrostatic pressure and tissue hydration (37). However, the introduction of a structured interstitium requires that an additional term of the fractional void volume of each phase, \( \chi_i' \), should be added to the typical, pressure dependent function of the lymphatic absorption from phase i. Therefore, \( q_L^i \) can be calculated as follows:

\[
q_L^i = \begin{cases} 
\chi_i' \cdot q_{L0} \left( 1 + 0.6 \left( P_i - P_0^i \right) \right) & \text{for } P_i \geq P_0^i \\
\chi_i' \cdot q_{L0} & \text{for } P_i < P_0^i
\end{cases}
\]

where \( P_0^i \) is the initial interstitial hydrostatic pressure in phase i and \( q_{L0} \) is initial lymphatic absorption from the tissue. Note that at physiological equilibrium the net fluid inflow to the tissue \( q_L^i \) must be equal to 0. Therefore, the total lymphatic absorption from the tissue, \( q_{L0,Mscc} \), must be balanced by inflow of water through the capillary wall, and \( q_{L0,Mscc} \) can be calculated from Eq. 6 in the muscle layer. However, one has to take into account inhomogeneity in the lymphatics distribution within the tissue, i.e., a lack of lymphatic capillaries in the anatomic peritoneum, and their uniform distribution within the muscle layer. In this case, the initial lymphatic absorption from the tissue can be calculated as follows:

\[
q_L^i = \frac{g_{\text{PERL}}}{g_{\text{PERL}} + q_{L0,Mscc}}
\]

Let \( L_{a\alpha} \) and \( psa \) be the hydraulic conductance and diffusive permeability of the capillary wall, respectively, calculated according to the general theory of the transport through the capillary wall (30). The corresponding parameters in each phase i must be corrected for the inhomogeneity in the capillary distribution between peritoneum and muscle layer (\( g_{\text{PERL}} \)) and for the volume distribution between the phases (\( \chi_i' \)), since it reflects the distribution of the effective capillary surface between phases. Therefore, for phase i:

\[
(L_{a\alpha})^i_{\text{pore}} = \chi_i' \cdot g_{\text{PERL}} \cdot L_{a\alpha_{\text{pore}}}
\]

\[
(psa)^i_{\text{pore}} = \chi_i' \cdot g_{\text{PERL}} \cdot psa_{\text{pore}}
\]

The differences in the density of the interstitium between anatomic peritoneum and muscle layer influence also formulas for the transport parameters between phases. The higher density of the interstitium in the peritoneum than in the muscle layer, would result in differences in the interphase hydraulic conductance, \( L_{a\alpha}^{1-2} \), and interphase diffusive permeability, \( psa^{1-2} \), between peritoneum and muscle layer. Let us assume that these parameters are not constant throughout the tissue, but they are \( a \) times greater in the peritoneum than in the muscle layer. In this case, they can be described using additional switching function \( a = (a - 1) g_{\text{PERL}} \) as follows:

\[
L_{a\alpha}^{1-2} = L_{a\alpha_{\text{Mscc}}} \left[ a - (a - 1) g_{\text{PERL}} \right]
\]

\[
(psa)^{1-2} = psa_{\text{Mscc}} \left[ a - (a - 1) g_{\text{PERL}} \right]
\]

where \( L_{a\alpha}^{1-2} \) is the interphase hydraulic conductance assumed in the muscle layer, and \( psa^{1-2} \) is the interphase diffusive permeability for the muscle. For example, for \( a = 2 \), \( L_{a\alpha}^{1-2} \) decreases from \( L_{a\alpha}^{1-2} = 2L_{a\alpha_{\text{Mscc}}} \) at the peritoneal surface, to the \( L_{a\alpha}^{1-2} = L_{a\alpha_{\text{Mscc}}} \) in the abdominal wall muscle.

The weighting factor of solute concentration difference across the capillary wall, \( f \), in Eq. 9, is assumed to be the same in both phases and calculated for each solute as:

\[
f = \frac{1}{Pe} - \frac{1}{\exp(Pe) - 1}
\]

\[
Pe = \frac{(1 - \sigma_{\text{EXP}}) q_{\text{EXP}}}{psa}
\]
The similar formulas for the interphase weighting factor from Eq. 10 can be calculated for each solute as:
\[
f^{-2} = \frac{1}{Pc^{1-2}} - \frac{1}{\exp(Pc^{1-2}) - 1}
\]
Eq. (22)

The general equations for the time evolution of tissue hydration and solute concentrations in the interstitial fluid can be derived from the classical nonequilibrium thermodynamic theory. It can be shown that time evolution of the interstitial fluid void volume ratio in each phase is given by:
\[
\frac{\partial q_i}{\partial t} = \frac{\partial q_i^1}{\partial x} + q_i^1 - q_i^{1-2} \quad (24)
\]
\[
\frac{\partial q_2}{\partial t} = \frac{\partial q_2^2}{\partial x} + q_2^2 - q_2^{1-2} \quad (25)
\]
where \(j_1^2\) and \(j_2^2\) are fluid fluxes through the phase \(F\) and \(C\), respectively; \(q_i^1\) and \(q_i^2\) correspond to the net fluid inflow from the external sources to phase \(F\) and \(C\), respectively; and \(q_i^{1-2}\) is the net fluid flow from phase \(F\) to phase \(C\). Moreover, based on animal experiments, the local functional relation between the total fluid void volume, \(\theta(t, x)\), and the interstitial hydrostatic pressure in phase \(i\), \(P(t, x)\), can be formulated as follows (37, 54):
\[
\theta(P) = \theta_{\text{MIN}} + \frac{\theta_{\text{MAX}} - \theta_{\text{MIN}}}{1 + \left(\frac{\theta_{\text{MAX}} - \theta_{\text{MIN}}}{\theta_{\text{MIN}} - \theta_{\text{MIN}}} - 1\right) e^{-\beta(P-P_0)}} \quad (26)
\]
where \(\theta_{\text{MIN}}\) and \(\theta_{\text{MAX}}\) are, respectively, minimal and maximal values of the fluid void volume, \(P_0\) is the initial fluid void volume for \(P = P_0\), \(\beta\) is constant, and \(P_0\) is the initial value of the interstitial hydrostatic pressure typically assumed 0 mmHg in modeling of peritoneal transport. Note that functional relation between \(\theta\) and interstitial pressure, \(P\) given by equation (26) allows for the further mathematical transformation of \(\frac{\partial \theta}{\partial t}\) to the system described by the time evolution of interstitial pressure 
\[
\frac{\partial \theta}{\partial t} \frac{\partial P}{\partial \theta}
\]
In addition, the time evolution of solute \(S\) concentration in the interstitial fluid of phase \(i\), \(C_i\), can be calculated from the mass balance equation in each phase \(i\) as:
\[
\frac{\partial (\theta_i C_i^n)}{\partial t} = \frac{\partial j_{i}^1}{\partial x} + q_{i}^1 - q_{i}^{1-2} \quad (27)
\]
\[
\frac{\partial (\theta_i C_i)}{\partial t} = \frac{\partial j_{i}^2}{\partial x} + q_{i}^2 + q_{i}^{1-2} \quad (28)
\]
where \(i\) is the phase index that can be either equal to phase \(F\) or phase \(C\); \(q_i^n\) is the solute void volume in phase \(i\), \(j_i^2\) is the solute flux across phase \(i\), \(q_i^i\) is the net solute flux into the phase \(i\) from internal source/sink, and \(q_i^{1-2}\) is the solute flux from phase \(F\) to phase \(C\).

Note that Eqs. 1–28 form a system of partial differential equations for fluid and solute transport through the two-phase structure of PTS interstitium, which can be solved numerically for the following initial and boundary conditions. It was assumed that initially both phases are in equilibrium, so the interstitial hydrostatic pressure and solute concentrations in the interstitial fluid in both phases are the same and the net fluid and solute flow between phases is equal to zero. The initial interstitial hydrostatic pressure in the interstitial fluid was assumed to be 0, i.e., \(t = 0\). \(P_i(0, x) = P_i(0, x) = 0\) mmHg. Moreover, it was assumed that glucose concentration in the interstitium was in equilibrium with blood, i.e., \(C_{gl}(0, x) = C_{b,G}\). The ratio of initial serum albumin concentration in the interstitium to its concentration in blood, \(Alb\), was calculated from the assumption that the net albumin inflow to the tissue from the external sources/sinks was equal to 0, i.e., \(q_{i}^{\text{cap}} = q_{i}^{\text{diss}}C_{alb}(x, t) = 0\). Therefore, the initial albumin concentration in each phase \(i\) was calculated as \(C_{alb}(0, t) = Alb\). The same initial conditions were valid in the muscle and in the anatomic peritoneum.

The conditions in the peritoneal cavity were assumed as in 3 min after the infusion of glucose 3.86% dialysis fluid and kept constant during numerical simulations. After fluid infusion into the peritoneal cavity, the hydrostatic pressure of the interstitial fluid at the peritoneal surface \((x = 0)\) is equal to the intraperitoneal hydrostatic pressure, i.e., \(P(t, 0) = P_0\), and the glucose concentration at the peritoneal surface was equal to that in dialysis fluid, i.e., \(C_{alb}(t, 0) = C_{b,G}\). Moreover, since there is no albumin in dialysate, \(C_{alb}(t, 0) = 0\). The external surface (for example, the skin of the abdominal wall muscle) was assumed to be impermeable to proteins, for glucose and fluid. Therefore, at the external surface, at \(x = x_{\text{MAX}}\), \(\frac{\partial P}{\partial x} = 0\), \(\frac{\partial C_{alb}}{\partial x} = 0\), and \(\frac{\partial C_{alb}}{\partial x} = 0\).

GRANTS
J. Stachowska-Pietka was supported by Polish Ministry of Science and Higher Education Grant N518 417736. Baxter Novum is the result of a grant from Baxter Healthcare Corporation to Karolinska Institutet.

DISCLOSURES
B. Lindholm is employed by Baxter Healthcare Corporation.

AUTHOR CONTRIBUTIONS
Author contributions: J.S.-P. and J.W. conception and design of research; J.S.-P., J.W., and M.F.F. analyzed data; J.S.-P., J.W., M.F.F., and B.L. interpreted results of experiments; J.S.-P. prepared figures; J.S.-P., J.W., M.F.F., and B.L. drafted manuscript; J.S.-P., J.W., M.F.F., and B.L. edited and revised manuscript; J.S.-P., J.W., M.F.F., and B.L. approved final version of manuscript.

REFERENCES


