Simulations of osmotic ultrafiltration failure in CAPD using a serial three-pore membrane/fiber matrix model

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Rippe B, Venturoli D. Simulations of osmotic ultrafiltration failure in CAPD using a serial three-pore membrane/fiber matrix model. Am J Physiol Renal Physiol 292: F1035–F1043, 2007. First published November 7, 2006; doi:10.1152/ajprenal.00251.2006.—Ultrafiltration failure (UFF) is a common complication of long-term peritoneal dialysis (PD). Functionally UFF is in most cases characterized by an enhanced peritoneal mass transfer area coefficient for glucose (PSg) combined with a largely unchanged peritoneal glucose osmotic conductance (LpS). Morphologically, marked UFF occurs with fibrosis of the submesothelial zone in the peritoneum, combined with vasculopathy and vascular proliferation in deeper tissues. To computer simulate UFF, changes both in the vasculature and in the interstitium have to be taken into account. For that purpose, we used a three-pore membrane/fiber matrix serial barrier model, applying the three-pore model to the capillaries and the fiber-matrix model to the interstitium. The parameters of the three-pore model have been published previously. The interstitial fiber density was set at 0.5% (vol/vol) and the fiber radius (r1) at 6 Å during control. If the interstitial fiber density was increased from 0.5 to 3%, and r1 to 7.5 Å (cf. collagen) while the capillary surface area was increased by 40% from control, then PSg increased from 9.3 to 11.5 ml/min, while the UF coefficient (LpS) was largely unchanged. Further increases in vascular surface area combined with further increases in fiber density caused further increments in PSg, whereas LpS remained unchanged. It is concluded that a matrix of fibers coupled in series with a three-pore membrane may be used for simulating the pathophysiological alterations occurring in the peritoneum in UFF, explaining the commonly observed “uncoupling” of small solute transport (PS) from the peritoneal UF coefficient (LpS) in this condition.

capillary permeability; fibrosis; interstitium; osmotic reflection coefficient; hydraulic conductance; glucose

ULTRAFILTRATION FAILURE (UFF) occurs in at least 30% of CAPD patients after 5 yr of treatment (9). Marked UFF is associated with fibrosis of the submesothelial zone of the peritoneum, which becomes avascular, usually combined with vasculopathy and vascular proliferation in deeper tissues (13, 37). Pathophysiologically, UFF is in a majority of cases characterized by an increase in small-solute transport [or dialysate-to-plasma concentration ratio (D/P) of creatinine] in the absence of large increments in the UF coefficient (LpS), or more precisely, in the peritoneal osmotic conductance to glucose (LpSσg) (4, 10). The enhanced glucose reabsorption in patients who show an increased transperitoneal small-solute transport, results in rapid dissipation of the glucose osmotic gradient during the dwell, causing a lower maximum UF volume and an earlier peak of the UF vs. time curve (10). Such alterations are incompatible with an increased vascular surface area alone, which would increase both the LpSσg and the transport of small solutes (PS for glucose) across the peritoneum. Mechanistically, these two changes tend to cancel, so that the height of the UF curve (maximum UF) would remain almost unchanged, but with an earlier “peak” of the curve (Fig. 1), when both PS and LpS increase to the same extent (10, 22). Only if there is an “uncoupling” between PS and LpS UFF will result. There are several potential mechanisms by which such an uncoupling can occur. Since small-solute transport is blood flow limited (29), while LpSσg is not (1, 18), an uncoupling between PSg and LpSσg may occur (to some extent) just because of increases in local peritoneal blood flow. Another possibility, directly correlating the morphological changes in the peritoneal membrane in long-term PD to the altered function, is the appearance of peritoneal neovascularization (13), and/or recruitment of microvessels in the peritoneum, together with fibrotic alterations in the tissue outside the capillaries (37).

In the present study, we investigate the functional impact of a combination of an increased small-solute mass transfer at the capillary level with ultrastructural (fibrotic) alterations of the interstitial tissue. Hence, we model the blood-peritoneal barrier as composed of two transport resistances coupled in series (33). The capillary wall is modeled using the planar three-pore model, whereas the interstitium is modeled as a second barrier outside the capillaries, normally having a low density of randomly oriented (glycosaminoglycan or proteoglycan) fibers of radius (r1) 6 Å (Fig. 2A). We then investigate the impact of increasing the effective vascular surface area (S) concomitantly with altering the fiber composition and by adding (collagen) fibers (r = 7.5 Å) to the interstitium. Interestingly, the deposition of fibers in the interstitium appears to be very efficient in reducing the UF capacity of the total capillary-interstitial barrier, while only little affecting small-solute transport (PS to glucose) and σg. Interstitial fibrosis may thus explain the uncoupling of PSg from LpSσg frequently observed in UFF.

METHODS

Porcine theory of peritoneal exchange. The three-pore model of peritoneal transport has been presented in detail previously (21, 22, 25, 34). According to this model, the equivalent peritoneal membrane is characterized as a membrane crossed by small pores, large pores and transcellular pores. The small pores, of radius (r) ~43–45 Å, approximately account for ~90% of the hydraulic conductance (LpS) and represent the main route of passage for small solutes (accounting for more than 99% of the total pore area for solute exchange), whereas 7–8% of the hydraulic conductance is accounted for by large pores (r ~ 250 Å), allowing the passage of macromolecules. Transcellular pores, representing a water-only conductive pathway [corresponding to aquaporin (AQP)-1], account for the remaining 2% of the hydraulic conductance. The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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The three-pore model has been successfully applied to large sets of experimental data in studies of fluid and solute exchanges in PD (22, 24, 26, 31, 32). The three-pore model is basically a nonasymmetric model, and therefore problems arise when it is applied to the disappearance of macromolecules from the peritoneal cavity to the peritoneal tissues (and to plasma). To account for the asymmetry of macromolecular transport, a modification of the three-pore model, i.e., a serial heteroporous peritoneal membrane model, has been developed (33). In this double-layered peritoneal equivalent membrane, the blood-facing side of the membrane had a small pore radius of 43 Å accounting for 90% of the UF coefficient, a large pore radius of 250 Å accounting for 8% of LpS, while aquaporins accounted for 2% of the total LpS. The best fitting serial heteroporous membrane (representing the interstitium) had a small pore radius of 67 Å accounting for 4% of the LpS, while the large pore radius was ~2,300 Å accounting for 95% of the LpS. In addition, 2% of total LpS was also represented by transcellular pores (33).

Serial pore membrane/fiber matrix model. The present strategy is similar to that taken in our previous publication (33) on serial peritoneal transport barriers, except that the membrane facing the dialysate side, i.e., the interstitium, is now modeled as a gel containing fibers similar in radius to proteoglycans (~6 Å). The reason we abandoned the pore model for describing the serial interstitial diffusion/filtration resistance is that a fiber matrix concept represents a more realistic model in describing the transport properties of the interstitium, especially when affected by fibrosis. Furthermore, an altered fiber matrix proved to be very efficient in increasing the interstitial filtration resistance compared with the corresponding small-solute diffusive resistance. Intuitively, according to the pore concept, convective transport would indeed be reduced more efficiently than small solute diffusive transport when the average (interstitial) large pore radius ($r^L$) is reduced (cf. fibrosis). Diffusion is namely dependent on the total pore (cross-sectional) area (proportional to $r^2$), while filtration events are dependent on the fourth power of the radius ($r^4$) according to Pouchuille’s law. Thus a 10-fold reduction in interstitial pore radius, while maintaining $A_0/\Delta X$ constant (by increasing the numbers of pores by a factor 100), will result in a hundredfold increase in filtration resistance. Simultaneously, small solute diffusion will be only moderately affected, since $A_0/\Delta X$ is unaltered and the degree of diffusion restriction to small solutes is only moderately reduced, by such a pore narrowing.

In the “classical” fiber matrix theory of capillary permeability, a matrix of fibers is postulated to account for the entire selectivity of the capillary wall by partly (or completely) filling out the spaces in between individual endothelial cells (the so-called interendothelial “clefts”) (14). A fiber matrix showing restrictive properties similar to that of most peripheral continuous capillaries (e.g., present in muscle, adipose tissue, connective tissue, and in the peritoneum), is typically

### A
**Three pore membrane with a normal (“loose”) serial fiber matrix**

| $\varepsilon = 0.995$ | $L_pS_0 \approx 3.66$ μL/min/mmHg |
| $r_f = 6$ (Å) | $PS_g = 9.30$ mL/min |
| $\sigma_g = 0.047$ | $L_pS = 0.078$ mL/min/mmHg |

### B
**Three pore membrane with a fibrotic (“dense”) serial fiber matrix**

| $\varepsilon = 0.96$ | $L_pS_0 \approx 3.02$ μL/min/mmHg |
| $r_f = 7.5$ (Å) | $PS_g = 13.46$ mL/min |
| $\sigma_g = 0.039$ | $L_pS = 0.078$ mL/min/mmHg |

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Fig. 1. Drained volume vs. time curves during control conditions using the basic (“lumped”) parameters of Table 4 (solid line), but where PS for glucose (PS$_g$) has been “inflated” (to 15.3 ml/min) according to (22, 25). Dotted line depicts the situation in which the vascular surface area is doubled, and hatched line depicts the situation in which “lumped” $A_0/\Delta X$ (PS for glucose) is doubled while keeping $L_pS$ unperturbed. Note that an increased vascular surface area alone will only marginally impact on the drained volume at 4 h, whereas an “uncoupling” of increases in $PS_g$ from $L_pS$ will cause marked reductions in drained volume at 4 h (ultrafiltration failure; UFF).

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Fig. 2. A: schematic illustration of a porous membrane (a three-pore membrane) series coupled with a “normal” interstitium containing a loose matrix of fibers. The capillary surface area is “normal” ($A_0/\Delta X = 23,660$ cm; $S = 1$). Overall transport parameters are in line with those used previously for simulations of an average patient (22) using the planar (noncomposite) three-pore model (Table 4). B: schematic illustration of a situation of simulated UFF. A dense fiber matrix has replaced the interstitium outside the capillaries. In this example, the capillary surface area is enlarged by 80%. Now, the mass transfer area coefficient for glucose (PS$_g$) is increased 45%, while $L_pS$ is completely unchanged and $\sigma_g$ moderately reduced (Table 5). The presence of a dense fiber matrix uncouples increases in small solute transport (PS$_g$) from $L_pS$. 

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In the “classical” fiber matrix theory of capillary permeability, a matrix of fibers is postulated to account for the entire selectivity of the capillary wall by partly (or completely) filling out the spaces in between individual endothelial cells (the so-called interendothelial “clefts”) (14). A fiber matrix showing restrictive properties similar to that of most peripheral continuous capillaries (e.g., present in muscle, adipose tissue, connective tissue, and in the peritoneum), is typically
one with a fiber density of 5–6% [void vol. (ε) 94–95%] and a fiber radius of 5–6 Å (14). We selected a much lower density of the assumed fiber matrix in the interstitium, namely 0.5% (void vol. ε) for the simple three-pore model. However, 0.06 is more or less exactly consistent with measured values of σ for glucose for continuous capillary walls proper (3, 19). By contrast, the overall (capillary-interstitial) UF coefficient was more or less identical to that characteristic of the capillary wall, i.e., of the three-pore model. The basic equations determining the permeability coefficients according to the pore theory, and according to the fiber matrix theory are shown in Tables 1 and 2, respectively. The series array permeability coefficients are evident from Table 3. A value of 5 is chosen for the so-called Kozeny coefficient (14). Mainly for the sake of simplicity the effects of “unstirred layers” were not included in our modeling. Furthermore, it is likely that the impact of the capillary wall and the interstitial transport barriers per se would (markedly) exceed that of nonmixed conditions in, e.g., the interstitium (6).

One inherent inconsistency in modeling capillary permeability using pore models is the commonly observed “mismatch” between $L_p S$ and PS. In whole organ settings PS, and hence, $A_0/\Delta X$ for glucose for continuous capillary walls proper is more or less exactly consistent with measured values of σ for glucose for continuous capillary walls proper (3, 19). By contrast, the overall (capillary-interstitial) UF coefficient was more or less identical to that characteristic of the capillary wall, i.e., of the three-pore model. The basic equations determining the permeability coefficients according to the pore theory, and according to the fiber matrix theory are shown in Tables 1 and 2, respectively. The series array permeability coefficients are evident from Table 3. A value of 5 is chosen for the so-called Kozeny coefficient (14). Mainly for the sake of simplicity the effects of “unstirred layers” were not included in our modeling. Furthermore, it is likely that the impact of the capillary wall and the interstitial transport barriers per se would (markedly) exceed that of nonmixed conditions in, e.g., the interstitium (6).

One inherent inconsistency in modeling capillary permeability using pore models is the commonly observed “mismatch” between $L_p S$ and PS. In whole organ settings PS, and hence, $A_0/\Delta X$, with the remarkable exception of the glomerular capillaries (12, 17), is markedly underestimated compared with $L_p S$ (23). The reason is that PS is extremely blood flow limited and sensitive to both the heterogeneity of pore configuration and the distribution of the capillaries in the interstitium. This reduces PS much below the “true” value (29). However, $L_p S$ is more or less unaffected by all the mentioned factors (1, 18). When $L_p S$ is calculated from a markedly underestimated $A_0/\Delta X$, this estimate will naturally become much lower than the value

### Table 1. Basic permeability coefficients according to the pore theory

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pore Theory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflection coefficient, $\sigma$</td>
<td>$1 - \frac{(1 - \lambda)^2 [2 - (1 - \lambda)] [1 - \frac{\lambda}{3}]^2}{1 - \frac{\lambda}{3} + \frac{2}{3} \lambda^2}$</td>
</tr>
<tr>
<td>Total reflection coefficient, $\sigma_{cap}$</td>
<td>$\alpha_c + \alpha_s \sigma_s + \alpha_l \sigma_l$</td>
</tr>
<tr>
<td>Free diffusion coefficient, $D_w$</td>
<td>$\frac{RT}{6 \pi \eta N_A \mu}$</td>
</tr>
<tr>
<td>Diffusive restrictive function, $A/A_0$</td>
<td>$\frac{(1 - \lambda)^{\frac{\epsilon}{2}}}{1 - 0.3956 \lambda + 1.0616 \lambda^2}$</td>
</tr>
<tr>
<td>Large pore fractional pore area, $A_L$</td>
<td>$\frac{\alpha_L}{1 - \alpha_L} \times \left( \frac{r_S}{r_L} \right)^2$</td>
</tr>
<tr>
<td>Permeability-surface area product (ml/min), PS or MTAC*</td>
<td>$\frac{A}{A_0} \times \frac{A_0}{\Delta X} \times D_w$</td>
</tr>
<tr>
<td>Total permeability-surface area product, $PS_{cap^*}$</td>
<td>$\left[ (1 - A_L) \times \left( \frac{A}{A_0} \right) + \alpha_L \times \left( \frac{A}{A_0} \right) \right] \times \frac{A_0}{\Delta X} \times D_w$</td>
</tr>
<tr>
<td>Capillary hydraulic conductance (ml · min⁻¹ · mmHg), $L_p S_{cap}^\dagger$</td>
<td>$\frac{A_0}{\Delta X} \times \frac{r_S^2}{8 \eta} \times \frac{1 - \alpha_s}{1 - \alpha_s - Z_{cap}}$</td>
</tr>
</tbody>
</table>

$\lambda = \frac{a_r}{a}$ where $a_r$ represents solute radius and $r$ stands for pore radius

$\eta$ water viscosity (0.007 dyn · s · cm⁻² at 37°C)

$A_0/\Delta X$ total unrestricted area of exchange per unit diffusion path length, cm

$\alpha$ fraction of total $L_p S$ (c = cells; $s$ = small pores; $l$ = large pores)

$\sigma$ reflection coefficient (c = cells; $s$ = small pores; $l$ = large pores)

RT product of gas constant and absolute temperature in degrees Kelvin

$N_A$ Avogadro’s number

$Z_{cap}$ capillary “inflation” factor to account for the discrepancy between $L_p S_{cap}$ calculated from $A_0/\Delta X$ (or $PS_{cap}$) and “true” (measured) $L_p S$.

*To convert PS to units of ml/min, the expression is multiplied by 60. †To convert $L_p S_{cap}$ to units of ml·min⁻¹·mmHg⁻¹, the expression is multiplied by 60 × 1,320.
an increased number of capillaries, or an increased blood flow, leading to interstitial changes in UFF, we assumed that there is either an increased capillary barrier into the three-pore model only partly corrects for the problem. To overcome this problem of discrepancy between \( A_0/x \) and \( J_{v,f} \), when calculated as inherent in the planar barrier model (20, 23). However, the complexity of modeling macromolecular transport increases markedly in a serial barrier model. Among other things, transport now becomes asymmetric, and furthermore, concentration polarization phenomena may potentially occur due to upconcentration of solute in between the (serial) barriers. Due to the complexity of macromolecular transport, we chose in the present study to focus only on the transport of fluid and of small solutes in UFF, leaving the treatment of large solute transport to a forthcoming publication.

A number of different scenarios are possible with respect to increases in capillary surface area and in fiber density, but generally speaking, the presence of an increasing density of fibers in the interstitium will tend to markedly reduce \( L_{pS,cap} \) (and macromolecular transport) while "sparring" \( PS_g \) (and \( \sigma_c \)) from being affected (reduced) when microvascular surface area is simultaneously increased.

### RESULTS

**Basic parameters.** The basic parameters selected are shown in Table 4 and Fig. 2A. In the serial barrier model 80% of the total small solute diffusion resistance of the composite barrier (reciprocal of \( PS_g \)) is offered by the capillary wall while 20% is offered by the interstitium. For the hydraulic conductance (\( L_{pS} \)) corresponding figures are 99.1 and 0.9%, respectively. It should be noted that total (capillary + matrix) \( \sigma_g \) is (markedly) reduced compared with that of the capillary

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fiber Matrix Theory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partition coefficient, ( \phi )</td>
<td>( \exp \left[ -\left( 1 - \varepsilon \frac{2a_r}{r} + \frac{a_r^2}{r^2} \right) \right] )</td>
</tr>
<tr>
<td>Restricted diffusion coefficient (cm(^2)/s) in fiber matrix, ( D_l )</td>
<td>( D_e \exp \left[ -\left( 1 - \varepsilon \right)^{1/2} \left( 1 + \frac{a_r}{r} \right) \right] )</td>
</tr>
<tr>
<td>Permeability-surface area product (ml/min) across the fiber matrix, ( P_{S_{fib}}* )</td>
<td>( \frac{A_g}{\Delta X} \frac{r^2}{4G_f(1 - \varepsilon)^2} Z_{cap} )</td>
</tr>
<tr>
<td>Hydraulic conductance (ml ( \cdot ) min(^{-1} ) \cdot mmHg(^{-1} )) across the fiber matrix, ( L_{pS_{fib}}* )</td>
<td>( 1 - \phi_b )</td>
</tr>
</tbody>
</table>

\( \varepsilon \), Fractional void volume \([ (1 - \varepsilon) = \text{fractional fiber volume}] ; a_r \), solute radius \( \bar{A} ; r_i \), fiber radius \( \bar{A} ; D_e \), free diffusion coefficient (cm\(^2\)/s), see Table 1; G, Kozeny coefficient (set at 5.0). *To convert \( PS \) to units of ml/min, the expression is multiplied by 60. †To convert \( L_{pS,cap} \) to units of ml\( \cdot \)min\(^{-1} \)\cdot mmHg\(^{-1} \), the expression is multiplied by \( 60 \times 1,320 \).

### Table 3. Basic permeability coefficients for a serial barrier model

<table>
<thead>
<tr>
<th>Series Array</th>
<th>( \frac{A_g}{\Delta X} ) cm</th>
<th>31,000</th>
<th>100,000</th>
<th>23,660</th>
</tr>
</thead>
<tbody>
<tr>
<td>( L_{pS,cap} ) ( \cdot ) ( L_{pS_{fib}}* )</td>
<td>( \frac{L_{pS,cap} \cdot L_{pS_{fib}}}{L_{pS,cap} + L_{pS_{fib}}} )</td>
<td>0.0786</td>
<td>8.02</td>
<td>0.0779</td>
</tr>
<tr>
<td>( P_{cap} ) ( \cdot ) ( P_{fib} )</td>
<td>( \frac{P_{cap} \cdot P_{fib}}{P_{cap} + P_{fib}} )</td>
<td>11.55</td>
<td>47.80</td>
<td>9.30</td>
</tr>
<tr>
<td>( P_{cap} ) ( \cdot ) ( P_{fib} )</td>
<td>( \frac{P_{cap} \cdot P_{fib}}{P_{cap} + P_{fib}} )</td>
<td>0.0583</td>
<td>0.00006</td>
<td>0.0470</td>
</tr>
<tr>
<td>( L_{pS_{fib}} ) ( \cdot ) ( \sigma_g )</td>
<td>( \frac{L_{pS_{fib}}}{\frac{\sigma_g}{P_{cap} + P_{fib}}} )</td>
<td>4.58</td>
<td>0.504</td>
<td>3.66</td>
</tr>
</tbody>
</table>

### Table 4. Basic parameters—serial three-pore/fiber matrix model

\( (\bar{A}) ; \frac{A_g}{\Delta X} = \) total unrestricted pore area over unit diffusion path length (cm); \( L_{pS} = \) UF coefficient; \( \sigma_c = \) reflection coefficient to glucose; \( L_{pS} \sigma_g = \) osmotic conductance to glucose. \( \varepsilon = 0.995 ; r_i = 6 \bar{A} \). Selection of capillary permeability characteristics: \( r_s = 43 \bar{A} ; r_b = 250 \bar{A} ; \alpha_s = 0.03 ; \alpha_c = 0.90 ; \alpha_c = 0.07 \).
wall alone due to the presence of the interstitium (0.047 for the two-layered barrier vs. 0.058 for the capillary barrier). Therefore, the fractional capillary LpS accounted for by small pores (\(\alpha_s\)) was, however, the same as in previous three-pore modeling using single membrane formalism.

Simulations of changes in capillary surface area (S) combined with increases in interstitial fiber thickness (\(r_f\)) and density (1-\(\epsilon\)). The situation described by Table 5 corresponds to a 40% increase in the capillary A0/\(X\) from 31,000 cm to 43,400 cm, while the interstitial A0/\(X\) is kept constant. Furthermore, the fiber density (1-\(\epsilon\)) is increased from 0.5% to 3%, and \(r_f\) from 6 to 7.5 Å, respectively, to account for a change in matrix composition from mostly proteoglycans to a more compact mesh of collagen fibers. Whereas an increased fiber density will increase restriction to transport, an increased fiber radius has the opposite effect. The net result is similar, in this case, an increased hindrance of the transport of water (and solutes) across the interstitium. Raising capillary barrier A0/\(X\) by 40%, the total (two-layered) A0/\(X\) was increased by 28% and total PS for glucose by ~25%, i.e., from 9.20 to 11.54 ml/min. At the same time, the composite LpS was almost unchanged, i.e., it increased by only 3%, and \(\sigma_g\) slightly dropped further to 0.031. In this situation the osmotic conductance to glucose was dramatically reduced to 2.39 \(\mu l\) \(\cdot\) \(\min^{-1}\) \(\cdot\) mmHg\(^{-1}\).

### Table 5. Permeability coefficients for a serial barrier model

<table>
<thead>
<tr>
<th>(A_0), cm</th>
<th>(\Delta X)</th>
<th>LpS, ml (\cdot) (\min^{-1}) (\cdot) mmHg(^{-1})</th>
<th>PSg, ml/min</th>
<th>(\sigma_g), (\mu l) (\cdot) (\min^{-1}) (\cdot) mmHg(^{-1})</th>
<th>LpS(\sigma_g), (\mu l) (\cdot) (\min^{-1}) (\cdot) mmHg(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capillary</td>
<td>Interstitium</td>
<td>Total</td>
<td>Basic total</td>
<td>Capillary</td>
<td>Interstitium</td>
</tr>
<tr>
<td>43,400</td>
<td>100,000</td>
<td>30,260</td>
<td>23,660</td>
<td>16.18</td>
<td>0.0013</td>
</tr>
<tr>
<td>55,800</td>
<td>100,000</td>
<td>35,815</td>
<td>23,660</td>
<td>20.80</td>
<td>0.0023</td>
</tr>
<tr>
<td>77,500</td>
<td>100,000</td>
<td>43,660</td>
<td>23,660</td>
<td>28.90</td>
<td>0.0035</td>
</tr>
</tbody>
</table>

\(\epsilon = 0.97; (A_0/\Delta X)_{Cap} \times 1.4; r_f = 7.5\) Å

\(\epsilon = 0.96; (A_0/\Delta X)_{Cap} \times 1.8; r_f = 7.5\) Å

\(\epsilon = 0.95; (A_0/\Delta X)_{Cap} \times 2.5; r_f = 7.5\) Å

Calculated parameters for the serial 3-pore/fiber matrix model assuming 3 scenarios of UFF in which A0/\(\Delta X\) and the fractional void volume (\(\epsilon\)) are concomitantly altered.
for glucose) is increased, although the number of aquaporins per unit capillary surface area is kept unperturbed in the modeling. In Fig. 5, A and B, the simulated rates of UF across the three separate pathways of the three-pore model are plotted as a function of dwell time under “normal” conditions (Fig. 2A and Table 4) and for the condition of UFF depicted in Fig. 2B (and Table 5). Note that the total UF is about equally partitioned among small pores and aquaporins, respectively, under normal conditions. The slightly higher fractional UF occurring through the aquaporins in the present simulations compared with that simulated by the classical three-pore modeling is due to the fact that \( \alpha_C \) was here set at a higher value (0.03) than in the classical three-pore model. In UFF (cf. Table 5), both the aquaporin-mediated water flow and the small pore UF were about equally reduced, although there was a tendency for a more pronounced relative reduction in small pore UF, especially at longer dwell times.

**DISCUSSION**

The essential result of the present simulations is that a serial three-pore membrane/fiber matrix model can be used for simulating peritoneal transport parameters under normal conditions and in situations similar to those of UFF. The latter condition is usually associated with an enhanced peritoneal mass transfer of small solutes in the absence of large increases in peritoneal UF coefficient (10). In most cases, UFF is morphologically associated with an increased number of microvessels (13) accompanying marked interstitial fibrosis, the latter preferentially affecting the submesothelial zone (37). The present simulations clearly demonstrate that interstitial fibrosis can very markedly reduce the overall UF coefficient of the
membrane and also reduce the osmotic reflection coefficient to glucose when the "effective" vascular surface area is concomitantly increased. At the same time, however, small solute transport is barely affected. This can explain why an increased "effective" vascular surface area combined with interstitial fibrosis may lead to increases in overall transperitoneal small solute transport, while the peritoneal ultrafiltration capacity is usually little affected.

Detailed analyses of the longitudinal PD cohort data of Davies (4), indicate that increases in PS for small solutes can be rather large over time in long-term PD and that PS is particularly increased in UFF. In the present study adjustments between increases in vascular surface area (S) and in matrix density (1-ε) were done to largely maintain LpS constant when both S and (1-ε) were increased. However, if changes in effective vascular surface area are effectively larger than those simulated here, then there would be less of uncoupling between PSg and LpS. By contrast, if changes in interstitial fiber matrix (collagen) deposition are more predominant, then there would be an exaggerated reduction of LpSg and hence, a larger uncoupling between PSg and LpS than obtained in the present simulations. Furthermore, we avoided the complication of mixing fibers of varying dimensions in our modeling both during control and UFF conditions. Had the fiber radius been fixed at 6 Å also for the UFF situation, the matrix effect on the uncoupling of PS from LpSg had been even more pronounced, i.e., it had occurred at a lower fiber density, than in the present simulations.

Data concerning exact correlations of morphological to functional peritoneal changes in UFF are essentially lacking. It is, for example, not known how increases in interstitial fiber density are actually matching the concomitant increases in vascular surface area. Particularly, the relationships between increases in small solute mass transfer area coefficients (PS) and in changes of the UF coefficient are not known in detail. In a recent study assessing solute transport in small chambers affixed to the parietal rat peritoneum, fluid and solute transport between the chamber fluid and the underlying peritoneal tissue was determined after 2 mo of subjecting rats (200–300 g) to increases in peritoneal thickness (marked) further reductions of LpSg (cf. Tables 1 and 2). The present article emphasizes the importance of the presence of structural changes in the interstitial avascular layer, i.e., an increase in density of the interstitial fibers, to create the observed dissociation between diffusive and convective transport changes occurring in UFF.

The results of the present study indicate that reductions in total (capillary + matrix) σg can occur due to moderate interstitial fibrosis, whereas more pronounced fibrosis can actually produce increases in σg (data not shown). Reductions in LpSg in the presence of an increased vascular surface area and fibrosis can thus be easily explained without invoking a reduced contribution of aquaporin-mediated water transport (αc). Already in the unperturbed (“normal”) situation the presence of a loose fiber matrix in the interstitium had a marked effect on the apparent fraction of LpS accounted for by aquaporins, so that the “apparent” (capillary + matrix) αc (Table 4) was actually considerably lower than the actual value of the capillary wall (11). Furthermore, in the presence of advanced interstitial fibrosis (marked) further reductions of LpSg occurred when modeled using the present principles.

The osmotic conductance for glucose has only been seldom assessed in clinical studies. A simple technique for the clinical evaluation of LpSg was introduced by Stell and Rippe (31), who measured a LpSg of 3.54 μl·min⁻¹·mmHg⁻¹ in 12 patients without UFF. Using a similar approach, Vonesh and Rippe (34) assessed a closely similar value (3.60 μl·min⁻¹·mmHg⁻¹) in five non-UFF patients. Applying a slightly different, more mathematical approach, Wanienski et al. (35) measured a 30% reduction in osmotic conductance in eight CAPD patients with permanent UFF and “high” small solute transfer, whereas three patients with UFF and a high fluid absorption rate displayed a rather unaltered osmotic conductance to glucose. According to the three-pore model, a high fluid absorption rate would be mainly dependent on an increased UF coefficient (LpS) of the peritoneal membrane (27, 31). Thus there may be a subgroup of patients with UFF in which the UF coefficient is (moderately) increased, while exhibiting an unchanged or moderately reduced LpS (cf. the scenario in Table 5). In these patients there may be a reduction in σg in excess of that predicted to occur following interstitial fibrosis. It has been suggested, supported by clinical data, that a reduction in the fractional LpS accounted for by aquaporins (αc) may be partly responsible for the UFF under such condi-

Flessner (5) recently discussed how an increase in thickness and “density” of the submesothelial, avascular compact zone, combined with an increased vascularity in deeper layers, would markedly increase the diffusive gradient across the peritoneal avascular tissue, thereby reducing the glucose concentration, and hence, the osmosis at the capillary walls. It was pointed out that diffusive transport could still be rapid across the avascular interstitial fibrotic layer, while UF may be more markedly affected (reduced) by the fibrosis. Although this reasoning is in principal agreement with ours, the statements were not founded on mathematical derivations provided in the article. Thus it should be pointed out that reductions in interstitial Δα/ΔX, due to just increases in transport path length (ΔX) would about equally increase the interstitial resistance to small solute diffusion and to convection (UF) in the present simulations (cf. Tables 1 and 2). The present article emphasizes the importance of the presence of structural changes in the interstitial avascular layer, i.e., an increase in density of the interstitial fibers, to create the observed dissociation between diffusive and convective transport changes occurring in UFF.
maintaining the cross-sectional interstitial pore area ($A_0$/interstitial large pore radius (down to capillary walls, as done in a previous study (33). Furthermore, a set of parallel large pores, positioned in series with the however, that the interstitium can be equally well described by ing the capillary barrier properties. It should be pointed out, reasons, we continue to apply the three-pore model for describ-

histological appearance of the interstitium, and for similar matrix modeling for the interstitial barrier, mainly due to the fiber matrix model, however, compared with pore models, is that it

freedom (the number of adjustable parameters) or its general behavior with respect to the nature of size-restriction or filtration resistance offered. Thus there is presently no way by which one can experimentally distinguish the fiber matrix model from the pore model. We have preferred to use fiber matrix modeling for the interstitial barrier, mainly due to the histological appearance of the interstitium, and for similar reasons, we continue to apply the three-pore model for describing the capillary barrier properties. It should be pointed out, however, that the interstitium can be equally well described by a set of parallel large pores, positioned in series with the capillary walls, as done in a previous study (33). Furthermore, interstitial fibrosis can be simulated by markedly reducing the interstitial large pore radius (down to =60–70 Å), while maintaining the cross-sectional interstitial pore area ($\Delta_0/\Delta X$) unaltered or just moderately reduced.

The presence of a fiber matrix outside the capillary wall may help to explain, not only the pathophysiological alterations occurring in UFF, but also how vectorial osmotic water flow can occur through the normal peritoneum. In the distributed model of peritoneal exchange (6) there is in PD a tissue glucose concentration gradient directed from the peritoneal cavity (the mesothelial surface) into ~200–400 μm of the peritoneal tissue. Superficial capillaries are thus exposed to a relatively high glucose concentration, producing a steep concentration gradient across the capillary walls. For progressively deeper capillaries, however, the transcapillary concentration gradients are correspondingly lower. Whatever magnitude of the transvascular osmotic concentration gradient, there is osmotic fluid flow across the capillary wall. This osmotic flow is directed toward the peritoneal cavity, guided by the tissue concentration gradient of glucose. How can this occur when the net hydraulic pressure gradient actually acts in the opposite direction (38)? An answer to this enigma may be that, in the presence of a fiber matrix in any infinitesimal volume of the interstitium, there is a partitioning of solute from water by the matrix, which actually produces osmosis in a direction opposite to the tissue glucose concentration gradient and opposite to the prevailing net hydraulic pressure gradient. In the present model the interstitial portion of the glucose osmotic conductance was well preserved during UFF due to the canceling effects of the progressive fall of interstitial $L_pS$ and the concomitant increase in interstitial $\sigma_0$ with increases in interstitial fiber density ($1-\epsilon$).

In conclusion, the present computer simulations indicate that a matrix of fibers positioned in series with a three-pore membrane may be used for simulating normal peritoneal transport characteristics and also the pathophysiological alterations occurring in the peritoneum in a majority of cases of UFF. An increased vascular surface area combined with an increased fiber density of the interstitium yields comparably large increases in small solute transport, while the changes in UF coefficient or the reflection coefficient to glucose are rather moderate. Thus a serial membrane-fiber matrix model may explain the hitherto puzzling “uncoupling” occurring between the increased small solute transport and the ratherunchanging peritoneal UF coefficient commonly observed in UFF.

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