Simulations of peritoneal solute transport during CAPD. Application of two-pore formalism

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Simulations of peritoneal solute transport during CAPD. Application of two-pore formalism. Blood peritoneal clearances of various endogenous solutes in patients undergoing continuous ambulatory peritoneal dialysis (CAPD) were evaluated according to recent developments of the two-pore theory of membrane permeability, using a non-linear transport formalism for the analysis. Based on results obtained from these calculations and taking lymphatic drainage into account, transport from peritoneal cavity to the blood was also simulated. With respect to solute transport the data were compatible with a functional blood-peritoneal barrier consisting of a two-pore membrane containing a large number of paracellular "small pores" of radius 40 to 55 Å and a small number of "large pores" of radius 200 to 300 Å. Solute smaller than 25 Å in radius were found to be permeating across the peritoneal membrane mainly by means of diffusion across the small pores, whereas solutes larger than 40 Å were calculated to reach the peritoneal cavity exclusively by unidirectional convection across the large pores. In addition, water was simulated to be transported through transcellular "ultrapores" (radius less than 8 Å) not accessible to hydrophilic solute permeation. Small solute absorption from the peritoneal cavity was found to occur by diffusion across small pores. Molecules larger than 25 to 30 Å in radius (molecular weight above 25,000) were simulated to be absorbed from the peritoneal cavity exclusively via non-size-selective lymphatic drainage.

In a majority of organs the selectivity of microvascular walls to hydrophilic solutes shows a bimodal pattern. With respect to solute transport capillary walls thus behave as artificial membranes, containing a large number of "small" protein-selective pores of radius 40 to 70 Å and a very small number of "large" (unselective) pores of radius 200 to 300 Å, as originally proposed by Grotte [1] and later corroborated [2]. Since the exchange properties of the mesenteric and peritoneal capillary walls seem to be of crucial importance for the exchange across the whole peritoneal membrane, the present article tested whether the blood-peritoneal barrier could be treated as a two-pore membrane as well. To model transperitoneal transport, recent developments of the two-pore theory were thus employed [3, 4] together with a non-linear flux formalism [5], and in addition the lymphatic drainage from the peritoneal cavity [6, 7] was taken into account. We also investigated the impact of a substantial transcellular flow of water (through very small pores) on transperitoneal exchange parameters.

In the study of Rippe, Stelin and Ahlémén [8] "unidirectional" solute clearance data obtained in patients undergoing CAPD were analyzed assuming that the transfer of both small and large solutes across the peritoneal membrane occurred mainly by means of diffusion. However, correct application of two-pore equations to transvascular solute transport data in general indicate that solutes larger than albumin permeate capillary walls more or less exclusively by convective (filtrative) processes and not by dissipative mechanisms [2—4, 9, 10]. Hence, the main purpose of the present study was to reevaluate the data of Rippe et al [8] according to recent developments of membrane transport theory. Furthermore, the validity of the two-pore model with respect to transperitoneal transport in general was tested on some previously published data on peritoneal protein transport during CAPD [11-13].

Methods

Theory and calculation techniques

The first step in a two-pore analysis of membrane transport involves the partitioning of net transmembrane filtration flow into the separate partial volume flows occurring across each set of pores. In a membrane containing a large number of small protein-restrictive pores (of radius 40 to 60 Å) and a few large pores (radius ≥ 150 Å) through which macromolecules can readily penetrate, any hydrostatic pressure gradient across the membrane will always cause filtration through the large pores, irrespective of the direction or magnitude of the volume flow through the predominating small pores. This is a result of the very low "effective" colloid osmotic pressure exerted by the proteins across the large pores, which in turn is due to the low protein reflection coefficients, σ', here [9, 10]. However, across the small pores, the protein reflection coefficients are near unity and here a nearly uncompromised effective colloid osmotic pressure gradient can normally counteract the hydrostatic pressure gradient, as predicted by the classical Starling hypothesis. When net filtration is zero, filtration of protein-rich fluid across

σ denotes the fraction of the ideal solute osmotic pressure gradient exerted across a semipermeable membrane, which is operative across a leaky membrane. σ equals 1 for a semipermeable membrane, from which the molecule is totally reflected, and σ equals zero if the membrane is freely permeable to the solute.
large pores is exactly counterbalanced by absorption of essentially protein-free fluid across small pores. At steady state, net filtration across the capillary walls (equalling the prevailing lymph flow) is about equally partitioned between small and large pores in a majority of organs [4, 10]. However, with increasing net filtration rates fluid flow will be progressively weighted towards the small pore system.

During CAPD a large osmotic gradient produced by glucose is employed to induce fluid flow across the peritoneal membrane. In this situation there could be a considerable flow of fluid across endothelial and mesothelial cells via pathways exclusive for water in excess of filtration through small and large pores. It is shown below, that if just slightly more than one per cent of the total peritoneal hydraulic conductance (ultrafiltration coefficient) is accounted for by a transcellular (water exclusive) pathway, as much as 35 to 50 per cent of the total fluid flux induced by glucose osmosis can occur through this pathway under conditions of CAPD.

We shall first use the method described by Rippe and Haraldsson [3, 4] to separate peritoneal small and large pore volume flows and solute fluxes (Model I). Later we shall remodel the data of Rippe et al [8] assuming that approximately 40 per cent of the glucose-induced osmotic fluid flow across the peritoneal membrane is due to transcellular water transport, not coupled to solute transport. Furthermore, the lymph flow from the peritoneal cavity [6, 7] will be taken into account in this modelling (Model II).

**Assessment of unidirectional peritoneal solute clearance**

In this article peritoneal transport during CAPD is dealt with in terms of "unidirectional clearance(s)" (Cl), because this parameter should closely reflect the transport characteristics of the peritoneal membrane under conditions when peritoneal transport is not markedly blood flow limited [8]. Cl is in principle independent of the intraperitoneal (i. p.) fluid volume ($V_D$) and of dwell time, and is defined as the plasma solute concentration ([8]) is obtained when $C_D = 0$ by dividing $J_s$ by ($C_B - C_D$). Hence, at zero transmembrane volume flow ($J_D$) across a homoporous membrane Cl equals the so-called "permeability-surface area product" (PS) or "mass transfer area coefficient" of the membrane as evident from:

$$J_s = Cl (C_B - C_D) = PS (C_B - C_D)$$  \hspace{1cm} (1a)

and

$$Cl = \frac{J_s}{C_B - C_D} = PS$$  \hspace{1cm} (1b)

$J_s$ equals the amount of solute accumulated intraperitoneally in the mean i. p. volume, $V_D$, per time unit during a short time period ($t_2 - t_1$):

$$J_s = \frac{V_D (C_{D_2} - C_{D_1})}{t_2 - t_1}$$  \hspace{1cm} (2)

where $C_{D_1}$ and $C_{D_2}$ are the i. p. solute concentrations at time $t_1$ and $t_2$, respectively. Inserting equation 2 in equation 1b yields:

$$Cl = \frac{V_D (C_{D_2} - C_{D_1})}{(t_2 - t_1) (C_B - C_D)}$$  \hspace{1cm} (3)

$C_D$ is here the mean i. p. solute concentration during ($t_2 - t_1$).

For short sampling periods, such as in the study of Rippe et al [8], $C_D$ can with negligible error be obtained as the arithmetic mean of $C_{D_1}$ and $C_{D_2}$. More correctly, $C_D$ may be expressed as the mean value of an exponential saturation curve of the type $C_D = C_B (1 - e^{-t})$, where $C_D$ is the i. p. concentration at time $t$, yielding [14, 15]:

$$Cl = \frac{V_D}{t_2 - t_1} \ln \frac{(C_B - C_{D_2})}{(C_B - C_{D_1})}$$  \hspace{1cm} (4)

Rippe et al [8] employed equation 3 (= eq. 4) to sample Cl values (in that article denoted PS values) also during conditions of net blood-to-peritoneal convection (filtration). Under these conditions transperitoneal solute flux can be regarded as the sum of a diffusive process and a convective process and $J_s$ can be described as [16]:

$$J_s = PS(C_B - C_D) + J_v (1 - \sigma) \bar{C}$$  \hspace{1cm} (5)

where $\bar{C}$ is the mean intramembrane solute concentration, which varies in a complex non-linear fashion as a function of $J_v (1 - \sigma)$ and PS according to the so-called non-linear solute flux equation (cf. eq. 8). For high values of PS (or low values of $J_v$), $\bar{C}$ will approach $(C_B + C_D)/2$, but for low values of PS (or high $J_v$) $\bar{C}$ will approach $C_B$.

The *theoretical* unidirectional plasma clearance of solute (Cl$_T$) is obtained when $C_D = 0$ by dividing $J_s$ by $C_B$. Setting $C_D = 0$ in equation 5 and dividing both sides of equation by $C_B$ yields:

$$Cl_T = PS + J_v (1 - \sigma) \bar{C}$$  \hspace{1cm} (6)

The unidirectional clearance defined according to equation 3 (or eq. 4) is closely similar to this theoretical unidirectional clearance and is obtained by dividing both sides of equation 5 by $(C_B - C_D)$:

$$Cl = PS + J_v (1 - \sigma) \frac{\bar{C}}{(C_B - C_D)}$$  \hspace{1cm} (7)

Thus, using equation 3 (or eq. 4) to obtain "unidirectional clearances", the convective term is overestimated by a factor $1/(1 - C_D/C_B)$. The error is, however, small because under the conditions of the study of Rippe et al [8], $C_D/C_B$ was close to zero for the large solutes studied ($\beta_2$-microglobulin and larger). For the small solutes investigated $C_D/C_B$ rarely exceeded 0.15. Hence, the convective term, contributing by only a few per cent to the total small solute clearances, was at maximum overestimated by 20 per cent.

Equation 6 is usually expressed in a form where Cl is dependent on $J_v (1 - \sigma)$ and PS instead of $\bar{C}$, which is more convenient for calculation purposes. This is known as the global non-linear (Patlak) flux equation [5], which is here modified to predict unidirectional clearances ($C_D = 0$):
using a Casio FX-850P computer. Clearances and volume flows
Cl values became minimal. All calculations were performed
versus ae curve to the experimental data. The best fit occurred
ix and r5 were varied so as to obtain the best fit of a specific r5
over pore radius (aefrs =
A/A0 =
Avogadro's number, while
constant and the temperature in degrees Kelvin and N is
diffusion restriction of a solute in a cylindrical pore, D is the
where D = R T/6 π η N a_s, and where A_s/Δx is the unrestricted area
diffusion distance. A/A_s is a term describing the diffusion
restriction of a solute in a cylindrical pore, D is the
solute diffusion coefficient, R T is the product of the gas
constant and the temperature in degrees Kelvin and N is
Avogadro’s number, while η is water viscosity (0.007
dyn−1·sec−1·cm−2). We employed the expression [10]:
A/A_o =
(1 − γ)^2 1 − 2.105γ 2 + 2.087γ^3 − 1.707γ^4 + 0.726γ^5
1 − 0.7586γ^5
(12)
to model the diffusion restriction as a function of solute radius
over pore radius (a_o/r_s = γ). Using an iterative procedure, A_s/
Δx and r_s were varied so as to obtain the best fit of a specific r_s
versus a_o curve to the experimental data. The best fit occurred
when the squared differences between measured and predicted
CI values became minimal. All calculations were performed
using a Casio FX-850P computer. Clearances and volume flows
from the study of Rippe et al [8] are all expressed in units of ml/
min/1.7m² body surface area (BSA).
Transport from the peritoneum to the blood (that is, in the
opposite direction) was simulated using the pore radii and A_s/
Δx resulting from the blood-peritoneal clearance simulations
and applying equation 8 for unidirectional transport (blood
concentration now assumed to be zero) for negative volume
flows. To the values obtained in this way (representing trans-
capillary solute absorption) blood uptake by non-size-selective
lymphatic drainage, amounting to liters ml/min, was added.
The estimated fraction of total peritoneal hydraulic conduc-
tivity (ultrafiltration coefficient, L_s) accounted for by large
pores (α_l) together with the calculated small and large pore
radii (r_s and r_l) were employed to compute the large pore to
small pore number ratio (n_l/n_s) and the large pore to small pore
surface area ratio (A_l/A_s) according to Poiseuille’s law [2–4]:

\[
\frac{n_l}{n_s} = \frac{\alpha_l r_l^4}{1 - \alpha_l r_l}
\]
(13a)
and
\[
\frac{A_l}{A_s} = \frac{\alpha_l r_l^2}{1 - \alpha_l r_l}
\]
(13b)

Model II. The two-pore solute flux analysis described above
can be further refined by considering the transcellular blood-
to-peritoneal flow of water caused by glucose induced osmosis
during the first few hours of a dwell for commercially
available peritoneal dialysates. Provided that a small fraction of
the total peritoneal hydraulic conductance (L_s) is accounted
for by a fluid conductive pathway exclusive for water and not
accessible to solutes, a surprisingly large fraction of the osmot-
ically-induced water flow will occur across this pathway, which
is assumed to be transcellular. The rationale of advancing
the analysis this far is to offer an explanation for the fact that
peritoneal small solute sieving coefficients measured in the
presence of a large glucose-induced osmotic flow are usually
very low, of the order of 0.6, and furthermore, that these values
remain rather invariant with increasing solute radius for solutes
smaller than 15 Å in radius [18].

The parameters necessary for a more detailed analysis of
transperitoneal exchange are obtained from the previous
analysis (Model I). The above analysis provided numbers on the
large pore radius (r_l) and the fluid flow occurring across the
large pores (J_l), and at least a preliminary number on the small
pore radius (r_s). The data of Rippe et al [8] yielded r_s = 47 (Å)
and r_l = 300 (Å). It is now possible using the theory for the
reflection coefficient (eq. 10) to simulate σ’s for glucose (σ_g)
and “total protein” (σ_prot) across small pores and large pores
separately, whereas solute reflection coefficients for the trans-
cellular pathway are assumed to be unity. In addition, to make
a detailed evaluation of the peritoneal fluid exchange, we need
to know the magnitude of the Starling forces, that is, the
microvascular-to-peritoneal hydrostatic pressure gradient (ΔP)
and the effective transperitoneal oncotic pressure gradient
(σ_protΔπ), and of the peritoneal hydraulic conductance. ΔP is in
most organs of the order of 10 — 17 mm Hg [10, 19], and we
have chosen a value of 13 mm Hg [4] in this simulation. For Δπ
we have chosen a value of 25 mm Hg for conditions prevailing
during CAPD. From a value of \(3.3 \times 10^{-3}\) of the osmotic conductance for glucose \((\sigma_g L_s)\) determined by Rippe et al. [20], it is possible to calculate an hydraulic conductance of 0.08 ml/min/mm Hg per 1.7 m² BSA in man, by assuming that the total reflection coefficient for glucose across the peritoneal membrane is 0.0432.

Assuming that the transperitoneal glucose concentration gradient \((\Delta C_g)\) and the Starling forces are the main determinants of fluid transport from the blood to the peritoneal cavity during peritoneal dialysis, fluid flow through any of the pathways mentioned \((J_{\text{net}})\) can be described by:

\[
J_{\text{net}} = \alpha_n L_p S (\Delta P - \sigma_{\text{prot.}, n} \Delta \pi - \Delta C_g \text{ R T } \sigma_{g,n}) \tag{14}
\]

where \(n\) refers to either small pores (s), large pores (L) or transcellular "ultra"-pores (c) and where RT has been defined above. \(\alpha_n\) denotes the fractional hydraulic conductance accounted for by either pore system, where \((\alpha_c + \alpha_s + \alpha_L) = 1.\)

\(\alpha_c\) can be calculated by setting the fractional transcellular glucose concentration as:

\[
J_{\text{transcell}} = 0.369 C_g - 1.265 \tag{18}
\]

Thus, for \(C_g = 13.6\) (such as, Dianeal 1.36%), the initial \(J_{\text{transcell}}\) becomes 3.20 ml/min, assuming that the dialysate is diluted to 85% of its initial concentration after i.p. instillation [6]. For \(C_g = 38.6\) (such as, Dianeal 3.86%), the initial \(J_{\text{transcell}}\) becomes 10.85 ml/min, which is in good agreement with measured initial net volume flow rates during CAPD [21].

Solving for \(C_g\) in equation 18 and inserting this expression into equations 16a through c yields:

\[
J_{\text{vL}} = 0.649 J_{\text{vnet}} + 0.178 \tag{19a}
\]

\[
J_{\text{vL}} = 0.350 J_{\text{vnet}} + 0.326 \tag{19b}
\]

\[
J_{\text{vL}} = 0.001 J_{\text{vnet}} + 0.052 \tag{19c}
\]

Thus when \(J_{\text{vnet}} = 0\), then \(J_{\text{vL}} = 0.2\), which corresponds to the normal peritoneal lymph flow [6]. Assuming that the lymph flow from the peritoneal cavity is instead 1 ml/min [7], equation 18 becomes:

\[
J_{\text{vnet}} = 0.314 C_g - 2.065 \tag{20}
\]

and the partial volume flows can be written as:

\[
J_{\text{vL}} = 0.649 J_{\text{vnet}} + 0.341 \tag{21a}
\]

\[
J_{\text{vL}} = 0.350 J_{\text{vnet}} + 0.607 \tag{21b}
\]

\[
J_{\text{vL}} = 0.001 J_{\text{vnet}} + 0.052 \tag{21c}
\]

We can now obtain appropriate values of \(J_{\text{vL}}\) for \(L = 0.2\) ml/min and 1.0 ml/min, respectively, according to Model II. Inserting the new \(J_{\text{vL}}\) values into equation 8 and making a parameter adaptation according to equations 10 to 12, the analysis can start over again to calculate small pore clearances \((C_{\text{IL}})\) and pore radius \((r_{\text{L}})\) are unchanged in this second analysis.

Sieving coefficients \((\phi)\) for various solutes across the peritoneal membrane as a whole are obtained from:

\[
\phi = \frac{C_{\text{IL}} + C_{\text{IL}}}{J_{\text{vnet}}} \tag{22}
\]

Results

Model I

Figure 1 shows a semi-logarithmic plot of simulated transperitoneal solute clearance versus molecular radius together with data from the study of Rippe et al. [8]. The simulated curve representing the "best fit" to experimental data was obtained for an "equivalent" small pore radius of 47 \(\AA\) and a large pore radius of 300 \(\AA\), and for an unrestricted pore area over pore length \((A_{\text{ps}}/A_{\text{ps}})\) of 46,000 cm. The total filtration rate was here set to 1 ml/min as prevailing during the experimental conditions of Rippe et al. [8]. Large pore filtration rate \((J_{\text{vL}} = 0.053\) ml/min/1.7 \(\text{m}^2\)) is obtained from the ordinate intercept of the large pore solute clearance \((C_{\text{IL}})\) versus \(a_c\) curve according to equation 9. Note that the difference between free diffusion \((r_{\text{f}} = \infty)\) and restricted diffusion across 47 \(\AA\) equivalent pores is very small for solutes smaller than vitamin B\(_{12}\) (molecular radius \(\approx 1.8\) \(\AA\)). According to equation 13 for \(a_{\text{IL}} = 0.056\) the large to small pore area number ratio becomes 27,700 and the large to small pore area ratio is calculated to be \(1.5 \times 10^{-3}\).

In Table 1 the experimental data shown in Figure 1 are compared with the simulated data on blood-peritoneal clear-
Heteroporous transport across the peritoneal membrane

Figure 1. Semi-logarithmic plot of transperitoneal clearance (Cl) versus molecular radius (a\textsubscript{\text{m}}) together with data from the study of Rippe et al [8]. Solid line is simulated for r\textsubscript{e} = 47 Å, r\textsubscript{L} = 300 Å and A/Δx = 46,000 (cm) at a total blood-to-peritoneal filtration rate of 1 ml/min/1.7 m\textsuperscript{2} BSA (Model I). Hatched lines show (for comparison) simulated data for pore radii different from those yielding the best curve fit to experimental data. Free diffusion across the small pores is denoted by r\textsubscript{e} = \infty and free convection across the large pores by r\textsubscript{L} = \infty. Large pore volume flow (J\textsubscript{V/L}) was 0.053 ml/min/1.7 m\textsuperscript{2}.

Table 1. Blood-to-peritoneal as clearance values computed to fit the data of Rippe et al. (1981) according to Model I

<table>
<thead>
<tr>
<th>Solute</th>
<th>Approximate mol. radius A</th>
<th>Measured clearance Cl/ml/min/1.7 m\textsuperscript{2}</th>
<th>Computed clearance Cl/ml/min/1.7 m\textsuperscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea</td>
<td>2.6</td>
<td>29.1 ± 1.7</td>
<td>28.07</td>
</tr>
<tr>
<td>Creatinine</td>
<td>3.0</td>
<td>23.3 ± 1.2</td>
<td>23.49</td>
</tr>
<tr>
<td>Glucose</td>
<td>3.7</td>
<td>16.5 ± 1.2</td>
<td>17.16*</td>
</tr>
<tr>
<td>β\textsubscript{2}-microglobulin</td>
<td>16.2</td>
<td>1.30 ± 0.16</td>
<td>1.22</td>
</tr>
<tr>
<td>Albumin</td>
<td>35.5</td>
<td>0.121 ± 0.0073</td>
<td>0.116</td>
</tr>
<tr>
<td>IgG</td>
<td>54</td>
<td>0.0456 ± 0.0049</td>
<td>0.0458</td>
</tr>
<tr>
<td>IgM</td>
<td>120</td>
<td>0.0275 ± 0.0026</td>
<td>0.0272</td>
</tr>
</tbody>
</table>

The best fit of experimental data to the two-pore model was obtained for r\textsubscript{e} = 47 Å, r\textsubscript{L} = 300 Å, A/Δx = 46,000 (cm) for a large pore volume flow of 0.053 ml/min and a total (net) transperitoneal volume flow of 1.00 ml/min.

* Glucose clearance was simulated as occurring from the peritoneal cavity to the blood.

ances (for r\textsubscript{e} = 47 Å and r\textsubscript{L} = 300 Å). Data simulation for glucose were performed for unidirectional transport occurring in the direction from the peritoneum to the blood, that is, against a blood-peritoneal convectional fluid flow of 1 ml/min.

Figure 2 shows in greater detail than Figure 1 the relationship between Cl and solute radius for solutes ranging in radius up to 16.5 Å (such as, β\textsubscript{2}-microglobulin) for blood-peritoneal transport (upper curve) and for transport from the peritoneum to blood (lower curve). The theoretical relationship describing free solute diffusion (r\textsubscript{e} = \infty) is also shown. A log-log diagram is here chosen to obtain a better graphic curve resolution than in Figure 1. Furthermore, approximate solute molecular weights (Mw) are plotted on the abscissa using an empirical (unpublished) relationship between solute radius and molecular weight (a\textsubscript{\text{m}} = 0.486 × Mw\textsuperscript{0.385}). According to the figure the maximal peritoneal clearance for urea is of the order of 30 ml/min. Solutes of the size of vitamin B\textsubscript{12} (such as, vancomycin) would, for example, have a transperitoneal clearance of approximately 5 ml/min, whereas insulin (Mw 5,000) is predicted to have a clearance of 2 to 3 ml/min. All these predictions are in close agreement with literature on measured unidirectional transperitoneal clearances [22–25]. Small solute clearances during dialysate flow limited conditions, that is, when solute is allowed to more or less completely equilibrate with the peritoneal fluid, are substantially lower than these unidirectional clearances (less than 9 to 10 ml/min), which are here simulated for conditions when i.p. solute concentrations are zero or near zero. As evident from Figure 2 the difference between unidirectional transport simulated for transport from the peritoneum to the blood against a convective flow and that in the opposite direction, is relatively small for solutes smaller than 15 Å.

Figure 3 shows large solute peritoneal clearance data from CAPD patients obtained from the study of Blumenkrantz et al [11] (Fig. 3A) and that of Young, Brownjohn and Parsons [12] (Fig. 3B) together with simulated best curve fits for each set of data (A/Δx = 46,000 cm). Clearances were obtained from the
published values of protein losses per day (in mg) for each protein during CAPD and their serum concentrations and calculations were performed according to equation 4. With the exception of \( \beta_2\)-microglobulin, data were selected for molecules being measured in both studies \([11, 12]\), namely albumin (A), transferrin (T), IgG, IgA, complement C3 and IgM. Effective time for peritoneal exchange during one day of CAPD was set to 1390 minutes (= 24 hours – 0.5 x the time for installation and drainage during four exchanges/day), and net blood-to-peritoneal filtration rate was set to 1 ml/min (1.4 liter negative i. p. fluid balance/day). Note the similarities between the two curves, which are not essentially different from that simulated for the data of Rippe et al \([8]\). In all three cases peritoneal albumin clearances (total protein), for example, is approximately 0.1 ml/min, a value found by several authors \([13, 26, 27]\). Also, the calculated volume flow occurring across the large pores was found to be approximately the same in the three studies (0.053 ml/min, 0.075 ml/min and 0.058 ml/min for the study of Rippe et al \([8]\), Blumenkrantz et al \([11]\) and Young et al \([12]\), respectively). The small pore radius estimation for the data of Blumenkrantz is less reliable than for the two other sets of data, since clearance data for \( \beta_2\)-microglobulin were missing here.

Recently Krediet et al \([13]\) published data on peritoneal protein clearances in diabetic and non-diabetic patients. Also in that study \( \beta_2\)-microglobulin data are missing, and furthermore, in the very large molecular size range clearance of \( \alpha_2\)-macroglobulin (mol radius = 90 Å) was monitored instead of that of IgM (approximate mol radius 120 Å \([2]\)). However, applying the present model for the analysis of peritoneal permselectivity to the data of Krediet et al (setting \( J_\psi = 1.0 \) ml/min; \( A_\psi/\Delta x = 46,000 \) cm) yielded a small pore radius of 44 Å, a large pore radius of 153 Å and a large pore volume flow during these conditions of 0.058 ml/min/1.7 m\(^2\). This is in good agreement with the results presented above.

**Model II**

Setting \( \alpha_5 \) to 0.015 results in a surprisingly large volume flow fraction accounted for by a water exclusive (transcellular) pathway \( (J_\psi/J_\nu) \) for glucose-induced osmotic flow, approximately 0.4, and hence the volume flow occurring through the small pore pathway is reduced in comparison with the Model I situation. Hence, setting \( J_\psi = 1.00 \) yields a value of \( J_\nu \) of only 0.471, and this will increase the \( r \) estimate from 47 Å to 52 Å for the data of Rippe et al when \( L \) is set to 0.2 ml/min. However, setting \( L = 1.00 \) \([7]\) results in a largely unchanged value of \( J_\nu \) (0.99 ml/min) and hence an unchanged \( r \) estimate (47 Å) for the same \( J_\psi \).

In Figure 4 solute clearance is simulated versus molecular radius according to Model II, setting \( L = 0.2 \) ml/min for transport occurring from the blood to the peritoneum (Curve A) and for transport in the opposite direction (Curve B), and for \( L = 1.00 \) ml/min for transport from blood to peritoneum (Curve C) and from peritoneum to blood (Curve D). In all cases \( J_\nu \) is 1 ml/min and \( A_\psi/\Delta x \) is 46,000 cm. The experimental data from the study of Rippe et al are also shown. Note that the four curves are almost identical for \( \alpha_5 < 10 \AA \), but simulations predict a highly asymmetric transport for solutes being larger than approximately 25 Å in radius, or more exactly, for \( \alpha_5 \) ≥ 30 when \( L \) is set to 0.2 ml/min and for \( \alpha_5 \) ≥ 20 when \( L \) is set to 1 ml/min.

In Figure 5 curve A of Figure 4 (dotted in Fig. 5) is simulated for different values of \( J_\nu \) ranging from zero to 10 ml/min/1.7 m\(^2\). The figure illustrates that changes in \( J_\nu \) are of little importance for solutes of the size of vitamin \( B_{12} \) (\( \alpha_5 = 8.4 \) Å) and smaller. For solutes of the size of albumin (hatched vertical line) effects of net convection are nearly maximal. Increasing
Fig. 4. Semi-log plot of solute clearance as a function of molecular radius employing the parameters fitting to the data of Rippe et al [8] according to Model II and assuming $J_{v,\infty}$ to be 1.00 ml/min/1.7 m$^2$ and $A_0/\Delta x$ to be 46,000 cm. Curves A and B represent clearances simulated for a peritoneal lymph flow of 0.2 ml/min and curves C and D for a lymph flow of 1.00 ml/min. Curves A ($r_s = 52$) and C ($r_s = 47$) are simulated for transport in the direction from the blood to the peritoneal cavity, whereas curves B and D show $C_l$ versus $\alpha_e$ for transport occurring in the opposite direction due to transcapillary and lymphatic absorption. Curve C deviates from curve A only for intermediate size solutes (molecular radius 15 to 52 Å) as denoted with a hatched line. Curves B and D illustrate the asymmetry of transport across the peritoneal membrane, being most pronounced for the simulated “high” lymph flow state ($L = 1$ ml/min; curve D).

$J_{v,\infty}$ from 0 to 1 (ml/min/1.7 m$^2$) implies, for instance, a doubling of albumin clearance from 0.054 to 0.12 (ml/min/1.7 m$^2$) and increasing $J_{v,\infty}$ to 3 (ml/min/1.7 m$^2$) implies another doubling of albumin clearance (to 0.28). The large pore curves are parallel and shift just moderately upwards for increasing net volume flows. These curves are shown in full only for the lowest and highest net filtration rates.

Figure 6 shows peritoneal sieving coefficients simulated for the data of Rippe et al [8] according to Model I ($r_s = 47$); and Model II ($r_s = 52$; $L = 0.2$) ($J_{v,\infty}$ = 1.00 and $A_0/\Delta x$ = 46,000). For Model II sieving coefficients remain relatively constant near 0.6 for small solutes ($\alpha_e \leq 10 - 15$ Å). In both cases small solute reflection coefficients conform to modern hydrodynamic theories (eq. 10). The osmotic reflection coefficient simulated for glucose for the peritoneal membrane as a whole is thus 0.038 for Model I and 0.043 for Model II.

Discussion

The essential result of the present analysis is that the blood-peritoneal barrier with respect to solute transport in man can be treated as a two-pore membrane containing a large number of small pores of radius 40 to 55 Å and a small number of large pores of radius 200 to 300 Å. Assuming that the peritoneal and mesenteric capillary walls are the principal structures responsible for the transport hindrance of solutes moving across the peritoneal membrane, these results imply that the permeselectivity of these capillaries is similar to that found in a majority of other continuous microvascular beds [2]. The small pores...
represent the major transvascular exchange pathway for small hydrophilic solutes and for water and account for at least 99% of the total pore area available for diffusion and approximately 93 to 94% of the total peritoneal filtration coefficient. The large pores, allowing for a slow unidirectional flux of macromolecules (and fluid) from the blood to the peritoneal cavity, can be calculated to contribute by only 0.15% to the total effective pore area available for small solute diffusion but account for as much as approximately 5 to 6% of the total peritoneal filtration coefficient.

Our analysis also shows that if just a very small fraction of the peritoneal hydraulic conductance is assumed to be accounted for by a water exclusive (transcellular) pathway rejecting solutes (Model II), a very large fractional volume flow will occur through this pathway under conditions of glucose induced osmosis. This explains why small solute sieving coefficients measured in the presence of a large osmotically-induced flow are low, approximately 0.6, for solutes ranging in size from urea to inulin (molecular radius 2.6 to 13 Å) [18]. It is indeed appropriate to consider the impact of at least some fluid flux occurring through a transcellular pathway, since \( \alpha_c \) has been determined to be 0.03 to 0.07 for a majority of continuous capillary endothelia [2, 28]. Furthermore, for the cat peritoneum as a whole Rippe, Perry and Granger [29] calculated a value of \( \alpha_c \) of approximately 0.01 in rough agreement with the value (0.015) employed in Model II of this study.

One earlier analysis of human peritoneal permeability has actually indicated the presence of abundant “ultrapores” (of radius 6 to 10 Å) accounting for nearly one-half of the peritoneal ultrafiltration flow, in addition to pores of an approximate radius of 40 Å [30]. In that analysis no pathways were, however, assigned to account for the important macromolecular passage across the peritoneal membrane. That model [30] is based on computer simulations of peritoneal permeabilities and osmotic reflection coefficients in CAPD patients, and unfortunately the numerical values of the \( \sigma \)’s employed do not conform to modern hydrodynamic theories [28], or to osmotic \( \sigma \) measurements performed in animal models [29, 31, 32] or in man [20]. The reason why reflection coefficients for small solutes were calculated to be as high as 0.4 to 0.5 in the publication of Nolph et al [30] is that these values seem to fit small solute sieving coefficients of the order of 0.6. By consid-

![Fig. 5. Semi-log plot of blood-peritoneal clearance versus \( \alpha_c \), simulated for different values of \( J_{\text{ve}} \), ranging from zero to 10 ml/min according to Model II. Parameters are identical to those used to simulate curve A in Fig. 4. (\( A_0/\Delta x = 46,000, \beta = 52, \gamma = 300, \alpha_e = 0.015, \alpha_l = 0.056, L = 0.2 \)). Small and large pore volume flows are simulated according to equations 19a and 19c, respectively.](image-url)
erating a large transcellular fluid flux it is possible, however, to account for these high sieving coefficients even for \( \sigma \)'s close to zero, which are predicted by current hydrodynamic theories for solutes smaller than 10 Å in radius (eq. 10).

The present two-pore analysis seems not only to yield consistent estimates of peritoneal permselectivity for a majority of previously published data on solute clearances in patients during CAPD. The model also fits data obtained in animal models. For the data of Hirszel et al [33] on dextran transport across the rabbit peritoneum (setting \( J_\nu = 0.17 \text{mL/min} \) as given in the paper, and setting \( A_0/\Delta x \) to 6,200 cm, as scaled from man to rabbit), we obtained a small pore radius of 43 Å and a large pore radius of 230 Å according to Model I. For the data of Arthurson [34] on rabbit peritoneal selectivity to dextrans the present analysis is more cumbersome, because the exact total filtration rate in this study is not given. A large pore radius estimation could however be performed, since it is essentially independent of net \( J_\nu \), yielding a value of 180 Å.

One disadvantage with the models presented in this article (Model I and Model II) is that they are “lumped parameter” models, treating the peritoneal barrier structures as a single “membrane”. Hence, they cannot predict, for instance, solute concentration gradients in the interstitium. Such models have been presented by Flessner et al [35-37]. Still the present analysis shows a good predictability as regards initial transperitoneal clearances and it may represent the “simplest” model that can describe clearances of both small and large solutes across the peritoneal membrane during CAPD with high accuracy.

The small pore radius determined from the data of Rippe et al [8] is, however, likely to be (slightly) overestimated. The reason is that the clearances of the smallest solutes investigated (urea, creatinine and glucose) in contrast to those of the larger solutes may be affected by “unstirred layer” effects outside the capillaries and also by blood flow limitation due to heterogeneity in peritoneal vascular arrangement and in flow. Heterogeneity is intrinsic in microvascular bed structure, and unstirred layers in the peritoneal dialysate and in the interstitium surrounding the capillaries cannot be avoided. Since we had no independent measurements of the peritoneal blood flow, or more specifically, of solute clearance as a function of blood flow, the underestimation of small solute clearances due to capillary heterogeneity could not be corrected for [38]. Neither did we correct for the “unstirred layer” effects. However, there is another way to evaluate approximately how much the small pore radius might have been overestimated. Thus, if the peritoneal small pore radius is much larger than 45 Å, the initial flux of albumin and “total protein” from blood to peritoneum during a markedly hypertonic dwell (such as, 3.86% glucose in the dialysate) becomes extremely high as based on theoretical calculations using the present model (Model II). Though, indeed, the flux of total protein (and albumin) has been reported to be markedly increased during the first two hours of a dwell [27, 39] the initial albumin clearance predicted to occur across 52 Å small pores during the first few minutes of a 3.86% glucose dwell \( (J_{\nu_w} \approx 10 \text{mL/min}; \text{Fig. 5}) \) is as high as 0.87 mL/min applying Model II \( (L = 0.2) \). This is seven to eight times as high as the normal peritoneal albumin clearance \( (= 0.1 \text{mL/min}) \) measured over longer time periods. Just reducing the small pore radius from 52 Å to approximately 45 Å (Model II) yields, however, an initial albumin clearance for an ultrafiltration rate of 10 mL/min in better agreement with measured values \( (0.2 \text{ to } 0.4 \text{ mL/min}) \).

According to the above reasoning the “simple” Model I calculations and the Model II calculations assuming a lymph flow of 1 mL/min seem to yield the most accurate predictions of \( r_s \) (and \( r_L \)). This may, however, be fortuitous, since in both these calculations the small pore volume flow may have been
overestimated, which tends to reduce the \( r_1 \) estimate. From a theoretical point of view Model II with an assumed lymph flow of 0.2 ml/min [6] may be the most correct. However, since it is not settled at present whether \( L \) should be set to 0.2 ml/min, which reflects the peritoneal to blood lymphatic uptake of colloids [6, 40], or to 1 ml/min, which represents the disappearance of colloids from the peritoneal cavity [7] during non-steady state conditions, we have employed both \( L \) values in our calculations.

The data presented here suggest that the exchange characteristics of the peritoneal membrane as a whole are similar to those of continuous microvascular membranes in general [2]. Thus, the results indicate that it is the walls of the exchange vessels that are the main determinants of the peritoneal exchange, whereas the interstitium and the peritoneal mesothelium may be of less importance as transport barriers in the peritoneal membrane. Morphologically the small pores modelled here are thus probably represented by the slits (clefts) between individual endothelial cells in the microvessels. The exact morphological counterpart to the large pores has not yet been identified, but they may be represented either by interendothelial "gaps" similar to the mentioned clefts, but wider, or less likely, by transendothelial channels formed by fused plasmalemmal vesicles [reviewed in 41]. Neither in the present study nor in previous analyses of large solute transfer [4] have we found any positive evidence for the notion that transendothelial shuffling of plasma proteins via plasmalemmal vesicles (transcytosis) should be of any quantitative importance for the normal passage of solutes across microvascular walls.

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