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Pathways of fluid transport and reabsorption across the peritoneal membrane

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The three-pore model of peritoneal fluid transport predicts that once the osmotic gradient has dissipated, fluid reabsorption will be due to a combination of small-pore reabsorption driven by the intravascular oncotic pressure, and an underlying disappearance of fluid from the cavity by lymphatic drainage. Our study measured fluid transport by these pathways in the presence and absence of an osmotic gradient. Paired hypertonic and standard glucose-dwell studies were performed using radio-iodinated serum albumin as an intraperitoneal volume marker and changes in intraperitoneal sodium mass to determine small-pore versus transcellular fluid transport. Disappearance of iodinated albumin was considered to indicate lymphatic drainage. Variability in transcellular ultrafiltration was largely explained by the rate of small-solute transport across the membrane. In the absence of an osmotic gradient, fluid reabsorption occurred via the small-pore pathway, the rate being proportional to the small-solute transport characteristics of the membrane. In most cases, fluid removal from the peritoneal cavity by this pathway was faster than by lymphatic drainage. Our study shows that the three-pore model describes the pathways of peritoneal fluid transport well. In the presence of high solute transport, poor transcellular ultrafiltration was due to loss of the osmotic gradient and an enhanced small-pore reabsorption rate after this gradient dissipated.

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Fluid transport across the peritoneal membrane is best described in theoretical terms by the three-pore model as originally proposed by Rippe.[1] This model identifies four potential pathways, a transcellular, water-exclusive pore system, now clearly identified as endothelial aquaporins;[2,3] an intercellular population of small pores, responsible for diffusive transport of small solutes, including water;[4,5] large pores, identified as the pathway for macromolecular leakage into the peritoneal cavity driven by hydrostatic pressure gradients; and a lymphatic route responsible for a proportion of fluid, solute, and macromolecular reabsorption.

It is possible, using the combination of an intra-peritoneal volume marker and measured concentrations of low-molecular-weight solutes, especially sodium, to estimate the proportion of fluid transport occurring via these pathways at different time points during a typical dwell.[6] Using this approach, during hypertonic (3.86% glucose) standard peritoneal permeability analysis tests, the relative components of fluid transport during the early stages of the dwell, especially the first 60 min, have been found to agree closely with the predictions of the model.[7] Small pores contribute a little over 50% of the total ultrafiltration, with a between-patient rate variability that is proportional to the membrane transport characteristics; as predicted, aquaporin fluid transport is proportional to osmotic gradient.

The three-pore model also predicts that following osmotic equilibration, reabsorption of fluid will occur via two pathways, the lymphatics and the small pores due to oncotic pressure gradient. Agreement between empirical and theoretical data from the point of equilibration of the osmotic gradient, especially the subsequent net reabsorption phase of the dwell, is less clear. This is partly due to previous studies having utilized relatively short (4 h) exchanges with hypertonic solutions that are not best designed to interrogate the reabsorption phase of the cycle. Alternatively, there may be difficulties with the type of volume marker used and interpretation of whether its disappearance reflects effective lymphatic absorption rates or small-pore fluid transport. The purpose of this study was determine the pathways of fluid transport under high and low glucose concentrations, the latter allowing examination of the reabsorption phase as the osmotic gradient dissipates rapidly. A different volume marker (^{125}I-albumin) was used to compare and contrast

findings with previous studies. Finally, as the method for determining aquaporin versus small-pore fluid transport necessitates the use of a correction factor for the diffusion of sodium, the impact of using different small-solute mass transfer area coefficients (MTACs) for creatinine and urate was also assessed.

RESULTS

Patient demographics

Eight stable male peritoneal dialysis patients were studied; their mean age was 55 years and the average time on peritoneal dialysis therapy was 21 months. Solute transport status ranged from 0.542 to 0.801, with a mean of 0.69 as determined by the dialysate to plasma creatinine ratio at 4 h and body surface area from 1.73 to 2.28 m^2.

Intraperitoneal volume curves for fluid pathways

The net changes in intraperitoneal volume and the components of fluid transport via aquaporin, small-pore, and effective lymphatic reabsorption are shown in Figures 1 and 2 for 3.86 and 1.36% glucose concentration, respectively.

Ultrafiltration via different pathways. The average rates of ultrafiltration at different time periods during the 3.86% dwells, including the different pore pathways, are summarized in Table 1 and Figure 1. It can be seen that these are time dependent, with the proportion via small pores being 55–70% depending on the method of correction for sodium diffusion. As expected, failure to correct leads to a higher proportion being assigned to small pores; the correction resulted in increased estimates for transcellular ultrafiltration, and this was greater when using urate in the early part of the exchange and when using creatinine over the whole 240 min.

During the first part of the 3.86% dwell (30–60 min), the rate of ultrafiltration via the small pores positively correlated with solute transport, whereas transcellular ultrafiltration more strongly negatively correlated (Figure 3a). In contrast, average small-pore ultrafiltration over the whole dwell did not correlate with solute transport, whereas variability in transcellular fluid transport was strongly negatively correlated to small-solute transport rate (Figure 3b).

Reabsorption via different pathways. This is summarized in Figure 2. It can be seen that in the latter part of the dwell, significant fluid reabsorption occurs via the small-pore pathway, typically −1.34 (s.d. ± 0.97) ml min^{-1}. The rate of this fluid reabsorption, calculated from the individual gradients between 120, 180, and 240 min, strongly correlated to solute transport rate ($R = 0.78$, $P < 0.01$), indicating that patients with high transport absorbed fluid more rapidly (Figure 4). This correlation was observed whether or not the small-pore transport was corrected for diffusion, as effectively very little fluid reabsorption occurred via the transcellular pores, estimates being 0.31, 0.17, and 0.29 ml min^{-1} uncorrected or corrected for creatinine or urate diffusion, respectively.

The fluid reabsorption estimated to be via lymphatics (see Figures 1 and 2) was linear with time for both glucose

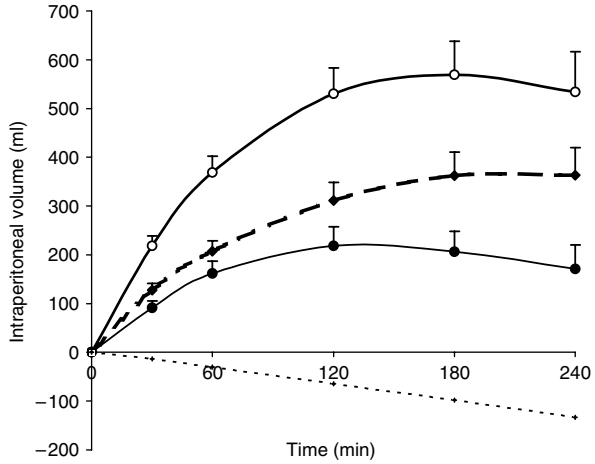

Figure 1 | Changes in net intraperitoneal volume (○) attributable to small-pore (◆), transcellular pore (●), and effective lymphatic (---) pathways using 3.86% glucose solution.

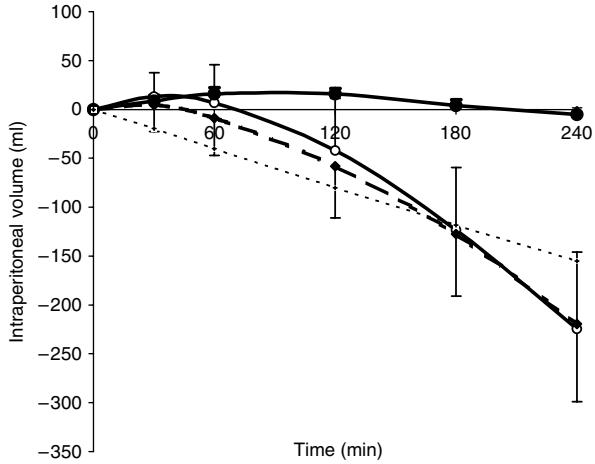

Figure 2 | Changes in net intraperitoneal volume (○) attributable to small-pore (◆), transcellular pore (●), and effective lymphatic (---) pathways using 1.36% glucose solution.

concentrations, the mean of the five estimates made in each patient being −0.65 ml min^{-1} (s.e.m. ± 0.19) for the 1.36% and −0.52 (± 0.22) ml min^{-1} for the 3.86% dwells. There was a weak but significant correlation between the rate of lymphatic absorption and solute transport for the 1.36% dwells, $R = 0.42$, $P < 0.05$, which was less significant in the 3.86% dwells, $R = 0.22$, $P = 0.05$.

DISCUSSION

These data are broadly supportive of the three-pore model of peritoneal fluid transport; they confirm previous observations of the relative fluid transport via the different proposed pathways in the ultrafiltration phase of a 3.86% exchange using a different intraperitoneal volume marker, and show convincingly for the first time the relative fluid reabsorption via small pores versus lymphatics. They also show that the

Table 1 | Mean ultrafiltration rates over 30, 60, and 240 min of 3.86% glucose exchange via different pathways with or without correction for diffusion

Mean ultrafiltration rate (ml min^{-1})	No correction for diffusion		Corrected using $MTAC_{urate}$		Corrected using $MTAC_{creatinine}$	
Total						
0–30 min	7.28 (1.9)		—		—	
0–60 min	6.15 (1.58)		—		—	
0–240 min	2.23 (1.0)		—		—	
Small pores						
0–30 min	4.6 (1.5)	***63%***	3.9 (2.0)	***53%***	4.23 (1.3)	***58%***
0–60 min	3.7 (1.1)	***60%***	3.36 (1.3)	***54%***	3.45 (1.03)	***56%***
0–240 min	1.67 (0.7)	***75%***	1.57 (0.7)	***71%***	1.51 (0.67)	***68%***
Transcellular pores						
0–30 min	2.67 (0.75)	***37%***	3.35 (2.2)	***46%***	3.05 (1.3)	***42%***
0–60 min	2.4 (0.84)	***39%***	2.78 (1.7)	***45%***	2.69 (1.2)	***44%***
0–240 min	0.55 (0.41)	***24%***	0.65 (0.64)	***29%***	0.71 (0.59)	***32%***

MTAC, mass transfer area coefficient.
Percentages=proportion of total ultrafiltration.
The bold italicized percentages equal the proportion of the total ultrafiltration via their pathway.

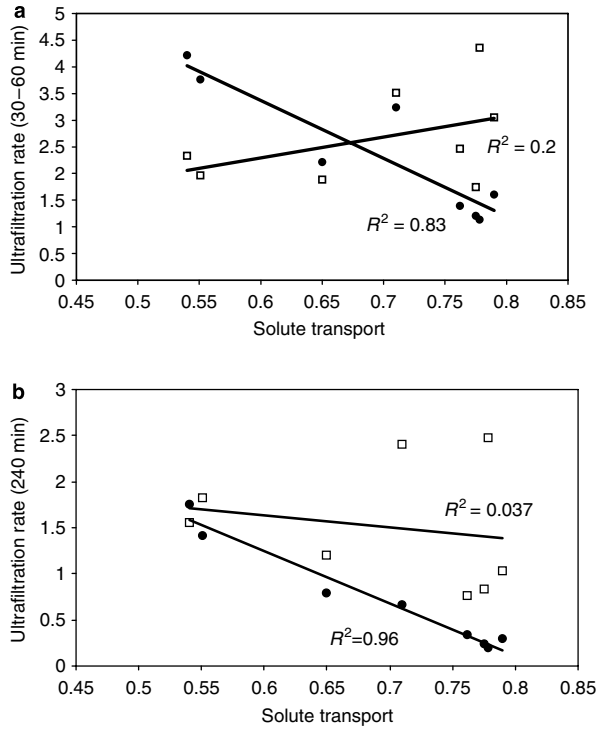

Figure 3 | Relationship of small-pore and transcellular pore ultrafiltration to transport status. Variability in ultrafiltration rate at (**a**) 30–60 min and at (**b**) 240 min attributable to solute transport characteristics of the membrane via the small-pore (□) and transcellular (●) pathways using 3.86% glucose.

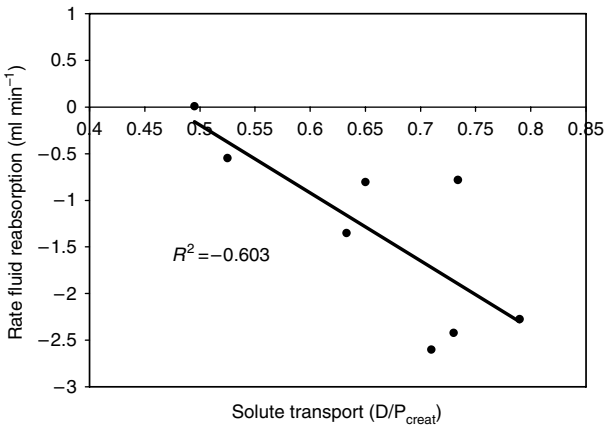

Figure 4 | Variability in the rate of fluid reabsorption (120–240 min) via small pores using 1.36% glucose solution.

influence of transport status on ultrafiltration is complex; while high solute transport is associated with increased ultrafiltration via small pores in the early stages of the exchange, this benefit is markedly outweighed by the negative effect on aquaporin fluid transport and the increased fluid reabsorption via small pores that occurs in longer dwells or when the osmotic gradient has dissipated.

The values obtained for total and relative ultrafiltration via the small-pore and aquaporin pathways during the first part of the 3.86% exchange were similar to those found previously using either dextran as an intraperitoneal volume marker or using simple volume drainage using the fast-fast peritoneal equilibration test.[6–8] As would be predicted from theoretical modeling, correction for diffusion of sodium, using either the MTAC for urate or creatinine, resulted in a reduction in the proportion of fluid estimated to pass via the small pores.[9] There has been debate as to which, if any, solute should be used for this correction. Close inspection of our data shows that the influence of correction differs according to the stage of the dwell, with urate resulting in a greater effect in the early part of the dwell, whereas using creatinine correction this increases as the dwell progresses. This difference is likely to reflect the relative difficulty we had in fitting urate diffusion–equilibration curves when calculating the MTAC for this solute, which did not always reach equilibrium during 4 h, probably due to the effects of charge on this molecule (Gibbs–Donnan effect). For the same reason, when urate was used for correction in the 1.36% glucose exchanges, it estimated that more fluid reabsorption was occurring via the aquaporins in the last part of the dwell compared with

estimation using creatinine for correction. It can be concluded that creatinine is preferable to urate as a correction factor, although it is likely that both lead to over-correction, as MTAC for sodium is probably much lower, at 4–6 ml min^{-1}. This remains controversial, as assumptions are made in estimating the Gibbs–Donnan effect, but for practical purposes, as suggested by La Milia[6] in the fast-fast peritoneal equilibration test, for short exchanges (1 h or less) the effect of diffusion can effectively be ignored.

The observation that small-pore fluid transport correlated positively with transport status in the first hour of the dwell, is in agreement with studies using dextran as an intraperitoneal volume marker.[7] This is in keeping with predictions of the three-pore model, as solute transport is effectively a measure of the small pore area in contact with dialysis fluid, and so patients with high transport status have a greater small pore area available for ultrafiltration via this pathway. This positive association of small-pore fluid transport and transport status was far outweighed by the negative association with transcellular fluid transport in the early part of the dwell. These two opposite effects of solute transport on ultrafiltration via different pathways early in the dwell might explain why no relationship with overall ultrafiltration was observed when using less complex models of membrane function.[10] This also confirms previous findings that by far osmotic gradient is the most important determinant of transcellular fluid transport. Indeed, it suggests that whereas small-pore fluid transport appears to be, to some extent, pore area-limited, this not the case for transcellular transport, indicating that there is relative redundancy in this pore system. This might also explain why a 50% reduction of aquaporin expression in hybrid knockout mice does not lead to a proportionate reduction in ultrafiltration,[3] and why aquaporin staining is not obviously reduced in severe ultrafiltration failure.[11] The reduced free water transport observed in severe ultrafiltration failure appears to be part of a more general reduction in ultrafiltration due to reduced osmotic conductance of the membrane affecting both pathways.[8] While comparing patients with and without ultrafiltration was not the purpose of this study, three of the subjects did have poor ultrafiltration as defined by net fluid removal on the 3.86% exchange <400 ml at 4 h. They had significantly higher small-solute transport ($MTAC_{creatinine}$ 11.4 ± 1.6 vs 7.3 ± 1.9 ml min^{-1}, $P = 0.02$), which entirely explained their lower transcellular transport at 60 min. At 240 min, it was net ultrafiltration via the small-pore pathway that differed the most (210 ± 33 vs 454 ± 131 ml, $P = 0.02$). In contrast to previous studies showing that small-pore fluid transport remains linear between 2 and 4 h of a 3.86% dwell,[7] a plateau or even a reversal of flow occurred toward the end of the dwell in the present study. This explained the relatively poor net small-pore ultrafiltration observed in the patients with ultrafiltration failure, whose peak ultrafiltration occurred between 120 and 180 min, whereas in the remaining subjects this had not occurred by 240 min.

This reversal of small-pore flow was much more easily seen in the 1.36% exchanges, where the rate was found to be proportional to the transport status or small pore area. The three-pore model predicts that once the osmotic gradient has dissipated, that net fluid reabsorption will occur via two pathways, the small pores, due to the oncotic pressure gradient, and the lymphatic pathways. Although these two pathways have long been acknowledged, there is considerable debate as to their relative importance.[12,13] In this study, fluid reabsorption via both pathways was proportional to the transport status, although this relationship was relatively stronger for that occurring via small pores. An association between transport status and effective lymphatic absorption rate has been found previously.[14] Bigger membranes are likely to have more lymphatics as well as more small pores, and so this might in part represent coupling due to size, but the present study also suggests that the absolute rate of fluid reabsorption is greater via small pores than via lymphatics, and that it is the between patient variability in small-pore reabsorption that results in the clinical problems associated with high transport. The relative contributions of lymphatic versus trans-capillary fluid reabsorption observed here are also compatible with predictions made from the distributed model for fluid reabsorption.[15] This model considers the membrane as a three-dimensional structure with capillaries embedded spatially within it.[16] It is possible to envisage that capillaries at different depths or at different points in their length, with different blood flows are associated with either ultrafiltration or back flow, as hypothesized by Ronco[17–19] and described here, via the small-pore pathway.

Part of the controversy over the relative importance of lymphatic verses small-pore pathways in fluid reabsorption relates to the methodological difficulties in measurement. Effective lymphatic absorption is inferred from disappearance of the large-molecular-weight molecules, although it is recognized that these may adsorb onto the peritoneal membrane and its interstitium, especially in the first few minutes of the dwell,[20] and it must be recognized that only a fraction of the marker disappearance directly enters the lymphatics. The estimate of 'lymphatic' flow in this study, using radio-iodinated serum albumin, was certainly less than that observed using dextran;[7,8,21] this was due to a relatively high recovery of radio-iodinated serum albumin. Whereas poor recoveries will lead to an overestimate of this pathway, it is difficult to see how the opposite might be occurring. It is possible, however, that an overestimate of fluid reabsorption by the lymphatics might lead to an underestimate of small-pore reabsorption in the latter part of a 3.86% dwell.

This study has emphasized the importance of small-pore fluid reabsorption as a cause of poor ultrafiltration and potentially frank ultrafiltration failure. One of the disadvantages of membrane function tests that concentrate on the early components of ultrafiltration, such as the peritoneal equilibration test (PET), mini-PETs, and standard peritoneal permeability analysis, is that they draw attention away from this aspect of poor net ultrafiltration. Fortunately there is

now a solution to this problem in the form of icodextrin; indeed, the observation that icodextrin, by counterbalancing the oncotic pressure gradient responsible for drawing fluid back across the small pores, leading to a relative clinical benefit that is greatest in high-transport patients, strongly supports the clinical importance of this pathway compared with lymphatics.[22] The recent finding that a glucose–icodextrin combination fluid results in additive effects lends further support to this mechanism[23] and underpins the value of mathematical modeling of the membrane in solution design that the present study has further validated.

MATERIALS AND METHODS

Study design and experimental protocol

Eight stable patients established on peritoneal dialysis with no recent episodes of peritonitis, but varying membrane function, were recruited. Paired, 240-min dwell studies were performed using either glucose 3.86% solution (Physioneal®; Baxter Healthcare, Thetford, UK) to investigate the early phase of osmotically driven ultrafiltration, or glucose 1.36% to examine the re-absorptive phase of fluid transport.

Each test exchange contained ^{125}radio-iodinated serum albumin (99% labeled, dose 90 kBq) as an intraperitoneal volume marker.[24] The test fluid was primed with 2 ml of 20% albumin to minimize tracer adhesion to the surrounding plastic and connections. During test exchange, frequent dialysate samples were drawn for measurement of solutes, including sodium, urea, urate, creatinine, and glucose; blood samples for solute analysis were taken at the beginning, at 60 min, and on completion of the 4-h test exchange. A subsequent shortened peritoneal exchange (rinse exchange), duration 45 min, was performed with 2 l of 1.36% glucose, normal pH, bicarbonate/lactate solution (Physioneal; Baxter Healthcare) to calculate peritoneal residual volume.[24] The study was approved by the local ethics committee after external peer review and patients gave written informed consent.

Analytical methods

Concentrations of solutes in dialysate and plasma were determined by a combination of enzymatic assay methods using an automated discrete random access analyser (DAX 72; Bayer Instruments, Basingstoke, UK), while sodium level was measured with the same equipment using the indirect ion electrode method, which, for dialysate, gave results equivalent to that of flame photometry in our laboratory. Plasma sodium was corrected for the Gibbs–Donnan effect, with a correction factor of 0.96. Dialysate creatinine levels were corrected for the effect of dialysate glucose concentration. Radioactivity was determined from triplicate samples using an Intertechnique Gamma counter. Background radiation was accounted for and the percentage error between each sample was within the order of 1 to 1.5%. Consistent reproducibility was demonstrated in our tracer technique, with recovery of isotope on completion of the peritoneal exchange averaging at 86.3% (s.d. ± 7.2)[24,25] calibrated against a pre-prepared standard for each individual experiment.

Calculations

Calculation of intraperitoneal volume profiles. The mathematical principles developed by Lindholm *et al.*[24] were employed to determine the apparent ($V_{a(t)}$) and actual ($V_{d(t)}$) intraperitoneal volumes during the course of the peritoneal exchange. Calculation of $V_{a(t)}$ (Equation (1)) assumes no loss of isotope from the peritoneal cavity, and will therefore overestimate peritoneal volume; this volume can be determined by measuring the radioactivity within the dialysate sample at any time point, $C_{r(t)}$, the initial instilled dialysate volume, V_0, and the initial radioactivity count, C_0. Significant volumes of fluid are drawn during the course of the peritoneal exchange for purposes of analysis and these were accounted for within the calculations:[24]

$$V_{a(t)}.C_{r(t)} = V_0C_0 \quad (1)$$

The calculation of the actual peritoneal volume, $V_{d(t)}$ (Equation (2)), uses first-order kinetics for the disappearance of the tracer molecule from the peritoneal cavity:

$$V_{d(t)} = \frac{V_{a(t)}(1 - (V_{a(T)} - (V_{out} + V_{res}))t)}{(V_{a(T)})} \quad T \quad (2)$$

Where V_{res} is the residual volume (estimated from the 'rinse exchange' following the 'test exchange'). $V_{a(T)}$ and V_{out} represent the final apparent volume and the final drained volume respectively and T is the duration of the 'test exchange'.

The net ultrafiltration of fluid was determined by subtracting the initial instilled fluid volume at the start of the peritoneal exchange from the calculated V_d, for purposes of standardization and to allow comparison of data, these values were normalized to an initial instilled volume of 2 l. The differences between the two calculated volumes, $V_{a(t)}$ and $V_{d(t)}$, during the course of the exchange exhibited a linear relationship and the calculated gradient of this slope represented the effective 'lymphatic' route reabsorption of fluid (L).

The best-fit exponential relationship as described by Rippe *et al.* (Equation (3))[26,27] was employed to describe individual volume profiles with greater precision. The best-fit volume at any time point, $V_{(t)}$, follows an exponential relationship, where V_0 defines the initial instilled peritoneal volume, while a_1, a_2, and k are coefficients defining this relationship. As repeat studies were conducted in each individual, it was possible to use the paired glucose data to determine a common value for a_2, for each individual, which was then incorporated into the unweighted least-squares method to determine the best-fit volume profiles.

$$V_{(t)} = V_0 + a_1(1 - e^{-kt}) - a_2t \quad (3)$$

Calculation of mass transfer area coefficient. The simplified Garred equation (see Equation (4)) was used to calculate the MTAC for solutes,[28] using the intraperitoneal volume (best-fit calculated volume, V_t) and dialysate (D_t) solute measurements at 120 min (min), as diffusive transport is maximal during this phase of the exchange.

$$MTAC = \frac{V_t}{t} \ln \frac{(V_0(P - D_0))}{(V_t(P - D_t))} \quad (4)$$

Calculation of small and transcellular fluid transport. The relative proportion of fluid transport via the small intercellular and transcellular pores was determined by the method of La Milia.[6] This is based on the principle that fluid transport via the small pores is accompanied by solute, for example, sodium, whereas transcellular fluid transport is water-selective. By knowing the intraperitoneal mass of sodium removed at any time point from Equation (5), small-pore fluid transport can be determined

from Equation (6):

$$Na^{+}{}_{\text{Removed}\,(t)} = (V_{d(t)}[Na^{+}_{(t)}]) - (V_{IN}[Na^{+}_{IN}]) \quad (5)$$

$$\text{Fluid transport small pores (ml)} = \frac{Na^{+}{}_{\text{Removed}\,(t)}\,1000}{[\text{plasma}\,Na^{+}]} \quad (6)$$

The diffusive component of sodium transport was corrected for using either the MTAC for creatinine or urate, or was left uncorrected (see text of results section). Transcellular fluid removal was calculated by subtracting small-pore fluid transport from the total.

Statistical analysis

Data are presented as mean values ± s.d. Linear regression was performed using Pearson correlation coefficient.

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